RENAL CORTICAL NECROSIS AND THE KIDNEY OF CONCEALED ACCIDENTAL HAEMORRHAGE

by

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PREFACE

This account of the renal lesions which follow concealed accidental haemorrhage is based to a great extent on the study of a series of cases at Glasgow Royal Maternity Hospital during the years 1935 to 1945. Very sincere thanks are due to my assistants there (Dr. M. D. Crawford and Dr. A. M. Stewart) who carried out some of these autopsies, and to all the clinical staff of the Hospital for their friendly and willing co-operation.

Though the analysis of these cases was primarily directed to the understanding of renal cortical necrosis, it has raised many problems on the broader subject of ischaemic damage to tissues. We have found that our own previous ideas on various aspects of general pathology were in need of considerable clarification, and sometimes of revision Among these aspects may be mentioned the autolytic changes that occur in dead tissues, the factors which control that autolysis, and the development of the different types of thrombosis. The conclusions reached here on these questions of general pathology are founded essentially on the study of the human material, but they are strongly supported by the results of a large series of animal experiments which we have carried out and which will be reported elsewhere.

The literature has been reviewed as fully as possible up to March 1952. Since the completion of this book, two excellent general textbooks on the kidney have been published: one by H. W Smith, *The Kidney, Structure and Function in Health and Disease*, New York, 1951; the other by A C. Allen, *The Kidney, Medical and Surgical Diseases*, London, 1952. These two authors do not deal in great detail with renal cortical necrosis nor with the histological effects of ischaemia on the kidney, but they give a full discussion of various other aspects of acute renal failure, and their conclusions merit serious study.

H. L Sheehan.

H. C. Moore.

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CHAPTER I

SCOPE OF THE INVESTIGATION

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cases have been reported, and good recent reviews of the subject have been given by Ash (1933), Gáspár (1938), Duff and More (1941), Dunn and Montgomery (1941), and Polayes (1941) The precise aetiology is still a matter of much debate, and there has been relatively little study of the early stages of the development of the lesion

Most cases of renal cortical necrosis follow the obstetric catastrophe which is known by various names· — concealed or mixed accidental haemorrhage, premature separation of the placenta, abruptio placentae, or uteroplacental apoplexy. (from this point on, the obstetric condition will be referred to as U.P.A , and renal cortical necrosis will be abbreviated to R C N.) The patients who develop R.C.N. usually die several days later, when the kidney lesion is in an advanced stage. In order to find the early histological stages of R C N., it is necessary to search among the kidneys of patients who die within the first day or two after the U.P.A., i.e. before there is any clinical evidence to indicate whether or not the renal cortex has been severely damaged

From such a study of the kidneys of a number of patients who have died at intervals from a few hours to several days after the U.P A , it is not difficult to recognise the early and the late examples of R.C.N , and to identify the various stages of the development of this lesion.

In addition, such a study reveals that, in those patients who do not develop classical R C N., there are a number of other acute renal lesions; the various stages of development of each of these lesions can also be identified These form the lesser grades of a series of lesions, which ...
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The present analysis of the pathology is based mainly on 67 patients who died following U P A. In addition, for purposes of general analysis, the records of 700 clinical cases of U.P.A. have been studied. The deaths among these 700 cases overlap to a great extent with the 67 autopsied cases, but it is important that the two series should not be confused

CHAPTER II

CONCEALED ACCIDENTAL HAEMORRHAGE; (U.P.A.)

GENERAL CLINICAL CONSIDERATIONS

It is necessary to give here a short summary of what is meant in this paper by the term U P.A . This condition varies greatly in incidence in different countries, and, in places where it is uncommon, some of the obstetricians do *not distinguish it very clearly* from "external accidental haemorrhage". Recent reviews have been given by Irving (1938), Young (1942a), McCain and Poliakoff (1949), Sexton et al. (1950), and Crichton (1950). A historical review was made by Holmes (1901)

In the present paper, the term is used in a strict sense. At some time during the last third of gestation, or very rarely a little earlier, the patient has a sudden onset of lower abdominal pain with a tense "woody" tender uterus. In most cases there is subsequently some external haemorrhage, which may be either bloody fluid or pure blood; the amount varies. The patient becomes shocked. There is a partial or complete suppression of urine, usually for only a short time but sometimes lasting several hours and occasionally much longer. The *first urine which is secreted after the U.P A is heavily loaded with albumen.* The foetus is stillborn, and there is massive retroplacental clot. Subperitoneal haemorrhages are present over the surface of the uterus, varying from small areas near the cornua up to gross lesions meriting the description of a "Couvelaire" uterus.

As with any disease process, there can be minor degrees which show less than the full picture. Such lesser cases are usually associated with only partial abruption of the placenta. They are basically similar to severe U.P.A., and differ from it only in quantitative aspects However, for the present study, no case has been accepted unless the clinical history followed the typical course and three pathological criteria were satisfied: — the death of the foetus, *the occurrence of gross retroplacental clot*, and, in all cases examined pathologically, the presence of subperitoneal haemorrhages over the uterus. In addition, every case where there was anything to suggest placenta praevia or rupture of the lower segment has been rejected.

Shock and haemorrhage The "shock" *is severe and is quite commonly* fatal. It is associated with considerable ante-partum blood loss; some of these patients have over 1000 gm. of retroplacental clot, which would correspond to 2 litres of whole blood. Atonic post-partum haemorrhage occurs in some of the cases, and can be a fatal complication *In the present series of autopsied cases* (a)

15 patients died undelivered; (b) 23 patients died within the first 12 hours after delivery, and among these there were 4 cases of moderate and 3 of very severe post-partum haemorrhage; this blood loss probably played some part in the fatal issue; (c) 29 patients died later in the puerperium; one of these patients had had a severe post-partum haemorrhage but had recovered from this blood loss. Sexton et al. (1950) did not have any deaths from atonic post-partum haemorrhage in their series of 476 cases of premature separation of "toxic" and "non-toxic" types

It is of interest that the blood pressure is usually well maintained during the stage of shock. Records are available in 38 cases from the present series; most of these cases were fatal within a few hours after the readings were taken. The blood pressure of these patients, while they were in a clinical condition of shock, ranged from 230/130 to 90/60, with a mean of 137/88. Dieckmann (1936) noted similar levels in non-fatal cases.

Aetiology and effects In nearly all the cases, the U.P.A has a sudden clinical onset without any local exciting factor. The condition is commonly treated by artificial rupture of the membranes, but this procedure does not appear to influence the pathological changes in the kidney in any way.

It is not clear how the U P.A. is related to the renal disturbance. It has been suggested (Browne, 1931; Young, 1942a) that the retention of retroplacental clot may be the direct cause. There are so many variable factors that it is difficult to get reliable evidence bearing on this explanation. An analysis of the present series of cases does not show any clear relation of the severity of the renal lesions to the duration of the retention of the retroplacental clot (the period from the onset of clinical symptoms to the delivery), nor to the amount of the retroplacental clot or of the other uterine haemorrhages. These negative findings can however not be accepted as of great significance.

There are occasional cases where the retroplacental haemorrhage appears to be produced purely by trauma and yet leads to severe renal damage. In the present series there were 3 patients who had version or bougie induction for oedema and slight hypertension. These three patients developed U.P.A after the obstetric interference and, though the clinical symptoms were relatively slight, there was retroplacental clot and subperitoneal haemorrhage over the uterus in all of them. The kidney lesions were indistinguishable from those following spontaneous U P.A ; one case had albuminuria casts and the other two had R C N The U P A. in these cases may have been caused directly by the interference, or may have been merely precipitated by the trauma. No definite deductions can be drawn from these three cases as to the possible role of retroplacental clot in causing renal damage.

In 4 of the patients, a slight external haemorrhage had occurred 10 to 26 days before the sudden onset of the U.P.A.. It seems possible that this may have had the same basis as the ultimate haemorrhage It was however not

accompanied by any significant clinical symptoms, and the kidneys in these cases showed no lesions sufficiently advanced to suggest an origin at the time of the preliminary haemorrhage.

CLINICAL STATISTICS OF U.P.A.

INCIDENCE

There were 700 cases of U.P.A. admitted to the hospital during the 12 year period 1932 to 1943. The total deliveries inside the hospital during that period numbered 38,600. The hospital admitted as emergencies all the complicated obstetric cases from its own district practice and very many of those from other parts of the town; calculations about various other obstetric complications indicate that each delivery in the hospital corresponded to about three deliveries in the region as a whole. The 700 cases of U.P.A. may therefore be taken as occurring in a gross total of about 115,000 deliveries; an incidence of 0.6 per cent in the region. Sexton et al (1950) record an incidence of 0.5 per cent of "toxic placental separation" in 40,000 deliveries in Boston.

The cases of U.P.A. showed a high incidence among multiparae, as will be seen from Table 1. This is in agreement with most previous observations in the literature. Batizfalvy (1937) recorded that 20 per cent of his cases occurred in the first pregnancy, 24 per cent in the second to the fourth, and 56 per cent in the fifth or subsequent pregnancy The corresponding percentages in the present series are 19, 32 and 49. The same aspect is reflected in the age of the patients, which in the present cases averaged 36 years. This is considerably higher than that of the general admissions to the hospital.

TABLE 1. *Relation of U.P.A. to parity*

Pregnancy	Total deliveries in hospital	Cases of U P A	Percentage with U P A
1	15,300	132	0.87
2 and 3	12,600	177	1.40
4 and 5	5,600	121	2.16
6 and over	5,100	270	5.30

The period of gestation at which the U.P.A. occurred is shown in Table 2. There is a high incidence as early as 28 to 31 weeks.

MATERNAL MORTALITY

There were 75 maternal deaths among these 700 cases; a maternal mortality of 10.7 per cent. As has been indicated earlier, all the foetuses died.

TABLE 2. *Relation of U.P.A. to gestation*

Weeks gestation	Cases of U.P.A.
23 to 27	10
28 to 31	123
32 to 35	189
36 to 39	236
Term	142

In the literature on accidental haemorrhage, the maternal mortality given by various authors ranges from 3 to 60 per cent. The discrepancy in the figures is the result of two factors:

(a) There are differences in the criteria of what constitutes U.P.A. or premature separation of the placenta. Some authors, as in the present paper, accept for analysis only those cases where the foetus dies, Crichton (1950) recorded a maternal mortality of 10.8 per cent in 120 cases of this type. Other authors include in their calculations not only cases of severe U.P.A. as defined here, but also milder examples of this complication, and even a number of cases which would commonly be classed as external or revealed accidental haemorrhage; a condition which carries a negligible maternal mortality and a relatively low foetal mortality. Thus Bland and Rakoff (1938) analysed 2319 cases of various types of accidental haemorrhage with 1539 foetal deaths and 146 maternal deaths; Crichton (1950) tabulated 807 cases by other authors with 468 foetal deaths and 48 maternal deaths, Sexton et al. (1950) recorded 200 cases of toxic placental separation with 104 foetal deaths and 12 maternal deaths; Browne (1951) analysed 655 cases at the Rotunda Hospital with 508 foetal deaths and 42 maternal deaths. If the maternal mortalities in each of these series are calculated against the foetal deaths, figures of 9.5, 10.3, 11.5 and 8.3 per cent are obtained. The average (9.5 per cent) is in reasonable agreement with the maternal mortality in the present series.

(b) Drastic surgery considerably increased the maternal mortality in the period before modern methods of treatment were introduced, as is shown by Crichton (1950). This accounts for the high death rates given by some authors reporting small series of cases. There are however not sufficient Caesarean section or hysterectomy deaths from that period to produce a significant alteration of the statistics from large series of cases.

It may therefore be concluded that the maternal mortality in the present group of cases is quite representative of that in cases of the same type in other clinics.

INCIDENCE OF RENAL FAILURE

An analysis of the 75 maternal deaths in the series of 700 clinical cases reveals certain points of importance. The primary division is into 52 cases dying from shock or haemorrhage during the first day after the U.P.A., and 23 cases dying later in the puerperium. The 52 early deaths may be subdivided on pathological grounds into (a) 27 where the kidneys showed no lesions or quite minor ones, (b) 25 with early but severe renal lesions. The puerperal deaths may be subdivided into (a) 17 due to renal failure, (b) 6 due to sepsis, pulmonary embolism or other cause, and in which the kidneys were not significantly damaged.

For the subdivision of the 52 early deaths, the kidneys of only 36 are available for histological examination Half of these showed either no lesions or such minor ones that there would presumably not have been any significant renal insufficiency in the puerperium. The other half had gross destructive lesions in the renal cortex which would probably have led to serious or fatal renal insufficiency in the puerperium if the patient had survived the first day; at least 7 of these had progressed to the early stage of R.C.N.. These 36 cases have been analysed according to the parity and gestation of the patients, and the results applied to the whole group of 52 early deaths. Though the figures for these 52 cases are based only on calculations, they are believed to give a reasonably correct representation of the true state of affairs. The figures for the 23 late deaths are those actually observed, and involve no calculations.

Table 3 shows the 75 maternal deaths analysed in this manner according to parity and gestation. The parity includes the pregnancy in which the U.P A. occurred, even if the patient died undelivered.

TABLE 3 *Relation of maternal deaths to parity and gestation*

	Total cases	Deaths			
		During first day		During puerperium	
		Little kidney damage	Severe kidney damage	Renal failure	Other causes
Parity					
1	132	3	4	2	1
2 and 3	177	4	3	8	1
4 and 5	121	5	3	5	0
6 and over	270	15	15	2	4
Gestation weeks					
23 to 31	133	3	5	9	0
32 to 35	189	6	7	5	1
36 to 39	236	8	10	3	4
Term	142	10	3	0	1

There are two salient features with regard to the *late* deaths from renal failure; i.e. after the first day of the puerperium.

(a) These deaths occurred mainly in 2 to 5 parae. The maternal mortality from this cause in primiparae was 1.5 per cent, in 2 to 5 parae was 4.4 per cent, and in 6 parae and over was 0 7 per cent.

(b) These deaths were more frequent when the U.P.A. occurred relatively early in the pregnancy than when it occurred near term. The maternal mortality in the late puerperium from this cause was 6.8 per cent when the U.P A. occurred at 23 to 31 weeks, 2.6 per cent at 32 to 35 weeks, 1.3 per cent at 36 to 39 weeks, and fell to zero at term.

These two features require more detailed consideration

Parity. The death rate from shock and haemorrhage during the first day after the U.P.A. is greater in the grand multiparae. The mortality on the first day is 5 3 per cent in primiparae, 4.0 per cent in 2 and 3 parae, 6.6 per cent in 4 and 5 parae, and 11.1 per cent in 6 parae and over.

As explained above, and shown in Table 3, in many of these early deaths there is pathological evidence of gross damage to the kidney, which would probably have led to death from renal failure in the puerperium if the patient had not died during the first day. When these cases are added to the actual deaths from renal failure in the puerperium, the total incidence of very severe damage to the kidney is 4.5 per cent in primiparae, and 6.2 to 6.6 per cent at all other parities.

The conclusions may therefore be reached (a) that parity has no significant influence on the incidence of gross renal damage, (b) that patients of 6 or greater parity are very liable to die of shock during the first day, and that, as a result, most of the grand multiparae who would have developed clinical evidence of R.C N. died too early to show this, (c) that a high proportion of the patients of 2 to 5 parity, who had severe damage to the kidneys, survived the first day and thus showed renal failure in the puerperium.

It will be clear that, if all the deaths during the first day could be prevented, the overall mortality from renal failure in the puerperium, which is at present 2 4 per cent, would rise to about double that figure.

Gestation. Similar considerations, applied to the period of gestation, show however that this factor has a real influence on the incidence of damage to the kidney

The mortality from shock during the first day rises gradually from 6 0 per cent in patients at 23 to 31 weeks gestation up to 9.1 per cent in patients at term. *When the cases with severe renal damage,* whether dying in the first day or later, are taken together, it will be seen that the incidence of this renal damage is 10.5 per cent in patients at 23 to 31 weeks, 6.3 per cent at 32 to 35 weeks, 5 5 per cent at 36 to 39 weeks, and only 2.1 per cent at term. No satisfactory explanation can be offered as to why the liability of the kidney to be

damaged in cases of U.P.A should be greater at 6 or 7 months gestation than at term.

In the literature there are about 70 maternal deaths which occurred after the first day, and in which clinical and pathological details are recorded. These cases are detailed in the subsequent chapters. The great majority of them are cases of R.C N.. The parities and gestations of these fatal cases are given in Table 4; there is no information as to the parity and gestation of the whole series of cases of U.P.A. from which they were drawn.

The parities show a similar distribution to that among the 700 cases of U.P A. discussed here; the high early mortality from shock among grand multiparae, which obscures this in the present series of fatal cases, appears not to have been operative. In general, the cases in the literature support the conclusion from the present series that there is no correlation between parity and kidney damage.

These cases of fatal renal failure in the literature show a very great preponderance among patients whose U.P.A occurred at 23 to 31 weeks. This is even more marked than in the present series, and emphasises the great danger to the kidney resulting from U.P A. at 6 or 7 months gestation.

TABLE 4. *Maternal deaths from renal failure after first day of puerperium recorded in the literature*

Parity	Number of cases
1	16
2 and 3	13
4 and 5	10
6 and over	20

Gestation, weeks	Number of cases
23 to 31	35
32 to 35	13
36 to 39	5
Term	1

PRE-EXISTENT HYPERTENSION AND TOXAEMIA

From this point onwards, consideration is given only to the autopsy group. In some of these cases there are adequate clinical records of ante-natal investigations. Many of the patients were however admitted to hospital as emergencies, and their clinical condition had not been studied before the onset of the U.P.A., though there are admission notes about the presence or absence of oedema, and of any obvious symptoms suggesting toxaemia. However, a full post-mortem examination was made in every case, so that the conclusions are in some ways more reliable than in a series based on clinical evidence alone.

CHRONIC HYPERTENSION

There was evidence of previous hypertension of some standing in 16 of the patients. The heart was increased in weight (range of 360 to 500 gm) and

showed hypertrophy of the left ventricle. There was usually gross fibrous thickening of the intima of large and small arteries in the kidney In 7 of these cases the blood pressure was taken during the stage of shock soon after the U P.A had occurred, and the systolic pressures were found to be 140, 150, 190, 200, 210, 210, and 220 mm. Hg Most of the patients had considerable oedema on admission, and some gave a characteristic history of the recent development of dyspnoea on exertion. Four of them had some pre-eclamptic symptoms, and their livers showed small periportal lesions of eclamptic type (Sheehan, 1950). Records of urine examination during the week before the U P A. are available in only two of the cases; both of these patients had albuminuria at that time.

PREGNANCY TOXAEMIA

Twelve patients had definite pregnancy toxaemia without any evidence of pre-existing chronic hypertension. These patients had hearts in the normal weight-range of 230 to 330 gm., and there was no unusual thickening of arteries in the kidneys In all of them the liver had periportal lesions of eclamptic type, though these were usually small and very scanty. Five of the patients had eclamptic convulsions; one had symptoms of pre-eclampsia; three had some hypertension and oedema and had had albuminuria during the week before the U.P.A , the remaining two had normal blood pressures and no oedema on admission Five of these patients had minor changes in the glomeruli of the type which is seen in eclampsia These eclamptic lesions will not be considered any further in the present paper

MINOR DISTURBANCES

Thirteen patients had some oedema on admission Five of these patients had been examined within two weeks before the U.P.A. and had been found to have slight to moderate hypertension, but only one had albuminuria None of this group of patients had any pathological evidence of hypertension or toxaemia, as judged from the heart, liver and kidney.

NORMAL

In the remaining 26 patients there was nothing to suggest any previous toxaemia or cardio-vasculo-renal disorder A few of the clinical records have incomplete data, but as far as can be ascertained, this group were free from previous oedema or other symptoms.

From this analysis it is clear that there are a large proportion of cases with no evidence of toxaemia or hypertension before the occurrence of the U.P A . Nevertheless these two conditions appear to be associated with U.P.A. rather commonly The occurrence of chronic hypertension in 16 patients out of 67

obstetric autopsies is very much higher than its incidence in routine obstetric autopsies, and must be accepted as significant.

The association of U.P.A. with pregnancy toxaemia is more debatable. The diagnosis of pregnancy toxaemia is primarily based here on the finding of periportal liver lesions of the type seen in eclampsia. It is, of course, open to argument whether these lesions do, in fact, necessarily indicate pregnancy toxaemia; this argument will not be pursued as it leads into the further discussion of the meaning of the phrase "pregnancy toxaemia". It may however be pointed out that, of the 16 cases of U.P.A. with these liver lesions, 5 had eclamptic convulsions and 5 had had previous symptoms of pre-eclampsia.

A more important consideration is whether this association of U.P.A. and pregnancy toxaemia is a chance one. In the routine obstetric autopsies of the hospital, about 8 or 10 per cent of the patients had died of eclampsia. The incidence of eclamptic convulsions in the fatal cases of U.P.A. (5 out of 67) was thus no higher than in the whole group of the fatal cases in the hospital. On the other hand the incidence of the liver lesions in U.P.A. is twice as great as in the routine obstetric autopsies. It would appear therefore that the association of pregnancy toxaemia with U.P.A. is too high to be merely coincidental. The reason for the association between the two conditions can only be a matter for speculation at present.

The relation between pregnancy toxaemia and U.P.A. has been stressed by many authors (Bartholomew et al., 1949). Premature separation was noted by Sexton et al. (1950) in 3 per cent of mild pre-eclampsias, in 14 per cent of severe pre-eclampsias, and in 37 per cent of cases of eclampsia. This raises the possibility that many of the cases of R.C.N which are recorded as following eclampsia have, in fact, followed U.P.A. associated with eclampsia. It may be noted in this connection that many cases of eclampsia have some subperitoneal haemorrhages at the cornua of the uterus; they have presumably had a vascular disturbance in the uterus similar to that which occurs in U.P.A., even though [illegible] kidney, [illegible] minor [illegible] le that these renal lesions were really from cases of U.P.A. associated with eclampsia.

In the present series, eclamptic lesions in the liver are relatively frequent in the patients who died during the first day or two after the U.P.A., and particularly in those who had early R.C.N. The reason for this is that patients who die early do so because of a combination of factors, of which severe toxaemia is certainly a common and important one. Patients who die later in the puerperium usually do not show these eclamptic lesions in the liver; if such lesions had developed, the toxaemia would have been so severe as to render unlikely the patient's survival until the late puerperium.

CHRONIC NEPHRITIS

In the literature it is frequently maintained, on the clinical grounds of previous hypertension and albuminuria, that many of the patients with U.P.A. have an antecedent chronic nephritis.

The pathological diagnosis of chronic nephritis requires that there shall be significant focal or diffuse scarring of the renal cortex, leading to the destruction of many nephrons. For the diagnosis of chronic glomerulonephritis there should, in addition, be evidence of glomerular lesions of some standing In the present series there was not a single case which could be accepted pathologically as an example of chronic nephritis. A detailed examination of the kidneys showed in 3 a few very small areas of reticular fibrosis in the outer cortex; this lesion was quite trivial, and could easily have been overlooked on ordinary examination One of these three patients had a chronic hypertension, one had a toxaemia, and the other had no clinical evidence of either condition. In addition there were 12 cases with occasional minute fibrous areas immediately beneath the renal capsule, representing the scars of surface nephrons which had been lost earlier in life. These are the ordinary changes which develop in the kidney with advancing years, and are no more than would be expected in any group of adult patients such as the present series.

A survey of the literature does not show any acceptable histological reports of chronic nephritis in cases of U.P A . Ivens (1928) recorded an early case [illegible] details. [illegible] es 2 and [illegible] 5), and Crichton (1950, 4 cases) None of these accounts have any histological data to support the diagnosis.

Several authors have recorded as "acute" or "subacute nephritis" the lesions which are seen in the healing stage around an area of R C.N., and which are described later in this paper. In some of these reports it was recognised that the lesions were purely secondary to the R.C N.; in others it was assumed that the lesions were pre-existent (Griffith and Herringham, 1906; Cruickshank, 1923; Davidson and Turner, 1930, Case 4, Dalrymple, 1930; Dingle, 1943, Case 1) Other authors have reported what appears to be the healing stage of proximal convoluted tubule necrosis or focal R.C N. under various titles, such as diffuse interstitial nephritis, nephrosclerosis, etc (Jardine and Kennedy, 1920, Case 11; Batisweiler, 1933, Case 2; Batizfalvy, 1937, Case 7; Adam, 1945, Case 6) In certain of these reports the histological descriptions are very meagre, so that it is possible that an occasional case may have been misinterpreted in the present analysis. It is not inconceivable that a patient with true chronic nephritis might develop U P.A. but, as far as pathological evidence is available, the association must be considered as an extreme rarity.

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in addition, be evidence of glomerular lesions of some standing. In the present series there was not a single case which could be accepted pathologically as an example of chronic nephritis A detailed examination of the kidneys showed in 3 a few very small areas of reticular fibrosis in the outer cortex; this lesion was quite trivial, and could easily have been overlooked on ordinary examination. One of these three patients had a chronic hypertension, one had a toxaemia, and the other had no clinical evidence of either condition. In addition there were 12 cases with occasional minute fibrous areas immediately beneath the renal capsule, representing the scars of surface nephrons which had been lost earlier in life. These are the ordinary changes which develop in the kidney with advancing years, and are no more than would be expected in any group of adult patients such as the present series

A survey of the literature does not show any acceptable histological reports of chronic nephritis in cases of U P.A.. Ivens (1928) recorded an early case where the kidney showed some chronic fibrosis, but she gives no further details Naked-eye reports of chronic nephritis are given by Knauer (1903, Cases 2 and 3), Pulvirenti (1908, Case 5), Frankl and Hiess (1921, Cases 4 and 5), and Crichton (1950, 4 cases). None of these accounts have any histological data to support the diagnosis

Several authors have recorded as "acute" or "subacute nephritis" the lesions which are seen in the healing stage around an area of R.C.N., and which are described later in this paper In some of these reports it was recognised that the lesions were purely secondary to the R.C.N., in others it was assumed that the lesions were pre-existent (Griffith and Herringham, 1906; Cruickshank, 1923; Davidson and Turner, 1930, Case 4, Dalrymple, 1930; Dingle, 1943, Case 1). Other authors have reported what appears to be the healing stage of proximal convoluted tubule necrosis or focal R C.N under various titles, such as diffuse interstitial nephritis, nephrosclerosis, etc. (Jardine and Kennedy, 1920, Case 11; Batisweiler, 1933, Case 2; Batizfalvy, 1937, Case 7; Adam, 1945, Case 6). In certain of these reports the histological descriptions are very meagre, so that it is possible that an occasional case may have been misinterpreted in the present analysis It is not inconceivable that a patient with true chronic nephritis might develop U.P.A. but, as far as pathological evidence is available, the association must be considered as an extreme rarity.

GENERAL PATHOLOGICAL LESIONS OF U.P.A.

This section does not include the renal lesions, as they are considered in detail later.

UTERUS AND APPENDAGES

In patients who were undelivered, the retroplacental clot remained *in situ*. Subperitoneal haemorrhages were observed over the uterus in every case. These haemorrhages were most marked near the cornua but, in the most extensive examples, they were scattered over any part of the upper segment. There was usually some haemorrhage into the muscle in the region of these haemorrhages, though often quite superficial There was no relationship between the site of the retroplacental haemorrhage and that of the subperitoneal haemorrhages.

Haemorrhages had occurred into both broad ligaments in 10 cases and into *one broad ligament in 5 In 4 cases subperitoneal haemorrhage was present* over the Fallopian tubes and round ligaments, and in 2 cases into the substance of the ovaries. A spread of the haemorrhage under the peritoneum of the posterior wall of the pelvis had occurred in 3 cases; in 2 of these it had extended out of the pelvis into the lumbar region. In 8 patients there was a small or moderate amount of free blood in the peritoneal cavity. Multiple splits of the peritoneum over the posterior surface of the upper segment of the uterus were present in 5 cases, and over both anterior and posterior surfaces in one. Oedema fluid, which was commonly blood-stained, was present in the parametria and broad ligaments in 14 cases. There was some ascitic fluid in 8 patients.

The condition of the placenta will not be considered here, as it has been amply described by numerous other authors.

SHOCK LESIONS

When the patient had died in shock, the pathological lesions usually associated with this condition were found (Sheehan, 1948a and 1948b). The subendocardial haemorrhages were usually prominent, but the flares of congestion near the centres of the liver lobules were rather more variable in incidence. The pituitaries of 24 of these cases have been examined histologically, but only 6 were later than 12 hours after the U.P.A.; i.e. at a time when pituitary lesions are sufficiently advanced to be recognisable. Necrosis of the anterior lobe was present in 3 of them It may be noted that R.C.N. was present in the 3 cases without pituitary necrosis, and in one of the cases that showed this lesion. Pituitary necrosis in association with R.C.N. has been noted by Young (1942b), Sheldon and Hertig (1942), Tomlinson (1945), Hugin (1946), Doniach and Walker (1946), Grasby (1947), Joekes and Bull (1948), and MacGillivray (1950). It appears to be purely a result of the shock which develops after the U.P.A.

LIVER

As mentioned above, small periportal liver lesions of eclamptic type were observed in 16 patients. Eclamptic lesions in the liver have been recorded in cases of R C N by Jardine and Kennedy (1913), Fordyce and Johnstone (1921), Matthias and Pincsohn (1925), Louros (1926), Reyna (1936), Vilk (1938), Young (1942b), and Bryce-Smith et al (1949).

Very early liver lesions of a different kind ... d
late in the puerp... d
o ...
T ... ...ained, but they were clearly
oi

There were however three types of lesions which appear to be more directly related to the U P.A :

(a) Two cases, at 5 and ...
of the liver, at such ...
the time of the U ... oten (1906).

(b) In two case ... small focal
necroses about 2 o ... These were pale and had red margins.

(c) Five cases had various stages of gross centrolobular necrosis, from the early changes at 12 hours up to healing lesions at 7 and 13 days These necroses all appeared to have begun at about the time of the U.P.A.. This lesion has been recorded by Bar and Kervily (1906), Bamforth (1923), Davidson and Turner (1930), Zalka (1933), Gáspár (1938), Garvin and Wezel (1938), Weaver and Haam (1939), Dieckmann (1942), Sheldon and Herne ..., Brown and Crane (1943), and Joekes and ...

These three ...
were found ... the kidneys as well as in
those with gr... They developed in one-seventh of the cases of U.P.A. and in a corresponding proportion of cases of R C.N. There is insufficient evidence to decide whether they were the results of the U.P.A. itself or of the factor that produced the U.P A

OTHER VISCERA

Lesions ...
with R ... leads to a
general ... disturbance, which may in one case be focussed particularly on the kidneys, in another on the liver, in another on the spleen, and so on This theory of splanchnic vasome... .
by Campbell and Henderson ...
of truth in it. Nev ... interpret as related
phenomena what ... be chance associations

Necrosis of the suprarenal cortex was observed in only one case of the present series; a case of proximal convoluted tubule necrosis. This suprarenal lesion is found in a variety of obstetric conditions (Crawford, 1951; Dewhurst, 1951); it has been recorded in cases of R.C N. by several authors: Chirié (1908), Jardine and Teacher (1911), Fahr (1934), Reyna (1936), Evans and Gilbert (1936), Weaver and Haam (1939), Sheldon and Hertig (1942), Dieckmann (1942), Brown and Crane (1943), Hertig and Mallory (1946), and Bryce-Smith et al (1949).

There were no examples of infarction of the spleen in the present obstetric series, but this condition was present in Case 72. It has also been recorded by Geipel (1925), Scriver and Oertel (1930), Hunt (1939), and Tuta and Vander-Kloot (1940).

Acute pancreatitis is seen occasionally in obstetric autopsies, especially in association with the toxaemias; it was recorded by French (1940) in a case of a man with R.C.N , but it was not observed in the present series.

Ulceration of the mucosa of the large intestine was observed in a few of the present cases, and has been recorded by some other authors. It may be uraemic, or it may be related to a vascular disturbance similar to that which causes the renal damage. The latter possibility is suggested by the frequency with which abdominal pain and diarrhoea herald the onset of R.C.N. in non-obstetric patients

In some of the present cases, foci of softening were observed in the basal ganglia or white matter of the cerebral hemispheres. These were similar to the lesions which are seen in some cases of hypertensive toxaemia, and the aetiology is presumably similar. These cerebral lesions may be responsible for the convulsions which sometimes develop early in the puerperium after U.P A.

CHAPTER III

GENERAL ASPECTS OF THE RENAL PATHOLOGY

Before the detailed description of the renal pathology is given, a few general considerations which apply to all the cases will be discussed here.

TECHNICAL METHODS

Clearly, in a study such as the present which deals with the death of tissues and with the subsequent necrosis-changes of these tissues, it is essential to avoid the complication of post-mortem autolysis This latter change occurs rapidly in the kidney, and leads to the swelling of epithelial cells and karyolysis which is frequently described as "cloudy swelling" For this reason, the present histological descriptions are based essentially on cases with early autopsy, i e. usually within 1 hour or, at most, within 2 hours after death There were however 21 cases where autopsy was delayed until 2 to 5 hours after death, and 18 cases with autopsy later than 5 hours after death. The histological sections from these delayed autopsies have been used only to provide confirmatory evidence about gross lesions which are less subject to post-mortem autolysis

The kidneys were removed with the greatest gentleness, only the peri-renal tissues being directly handled. Any part of the kidney which had even been lightly held during the cutting of the organ was not used for histology. This is important, because "sleeve-separation" or dissociation of tubular epithelium can be simulated by squeezing of the tissues.

Fresh kidney tissue which is still warm is grossly distorted by formalin fixation The tissues were therefore fixed in saturated mercuric chloride solution, followed by post-chromation Satisfactory frozen sections for fat staining can be made if the block is treated with iodine in 50 per cent spirit before cutting

GROUPING OF THE CASES

The kidneys of the 67 fatal cases show a variety of lesions which can be arranged in groups of ascending severity. A short summary of the grouping may make this clear

(1) At the lower end of the series are the cases which show no recognisable lesions

(2) Next are a group of cases with changes which are usually of a minor nature and indicative only of proteinuria. In a few of the cases, this leads to the formation of protein casts in the collecting tubules.

(3) The third group comprises two lesions: (a) A degenerative change in the

CHAPTER IV

RENAL LESIONS LESS SEVERE THAN CORTICAL NECROSIS

NO LESIONS

In some cases the kidney shows no histological abnormality. When the patient dies very soon after the U P A , the negative findings in the kidney may be explicable in two ways. There are a few cases where death occurs so early that there is not sufficient time for the development of histological changes, even such slight ones as the escape of protein through the glomeruli. In other cases, any minor renal changes which have occurred may be obscured by post-mortem autolysis and thus not be identifiable. Nevertheless, in view of the invariable occurrence of albuminuria in clinical cases, it must be accepted that the total absence of any renal disturbance in these rapidly fatal cases must be very rare

In patients who die later in the puerperium from some incidental complication, it is quite understandable that kidneys, which have had only trivial lesions after the U.P.A., should have completely recovered and thus show no histological abnormality at this late stage.

In the present group there are five patients who died during the first day after the U.P A. as a result of shock or blood loss, and two patients who died in the late puerperium as a result of pulmonary embolism. The kidneys microscopically showed no pathological lesions; in particular the tubular epithelium appeared healthy (Fig. 1). In three of the five patients who died early, the kidneys showed some post-mortem autolysis so that any minor pathological changes in the tubular epithelium would not be recognisable, but there were at any rate no identifiable lesions.

One of the other patients happened to have many multinucleated cells in the epithelium of the proximal convoluted tubules. This histological appearance is not very uncommon in middle-aged or old patients (Harman and Hogan, 1949); it has no relation at all to U.P.A.

Macroscopically the kidneys in this group appeared normal, with a mean weight of 150 gm.

CASE NOTES

In all the following case summaries, the details of the U.P.A itself are omitted. The parity includes the pregnancy at which the U.P.A. occurred, even in the cases where the patient died undelivered. The duration is the period from U.P A to death

CASE 1. Age 35, para 1, gestation 40 weeks, duration 6 hours. Very severe shock. No external haemorrhage. Delivered at 5 hours Moderate p p h. Died of shock 1 hr. p.p

CASE 2. Age 39, para 12, gestation 40 weeks, duration 9 hours. Shock and much external haemorrhage at 1 hour. Died undelivered. Complete anuria to death

CASE 3. Age 37, para 3, gestation 38 weeks, duration 12 hours. Slight external [illegible] Died undelivered

[illegible] No external
[illegible] sions in liver.
[illegible] lema for one
[illegible] l at 6 hours.

Placenta removed manually 10 hours p.p. Died of shock 21 hours p p. Complete anuria from ante-partum haemorrhage to death

CASE 6. Age 36, para 5, gestation 38 weeks, duration 9 days. Slight external haemorrhage and small retroplacental clot. Died of pulmonary embolism 9 days p p

CASE 7. Age 30, para 10, gestation 36 weeks, duration 27 days. Oedema and hypertension for 5 days previously. Some external haemorrhage. Died of pulmonary embolism 26 days p.p.

LITERATURE

In the literature there are a few reports where the kidneys of patients dying after U.P.A. were said to be normal apart from anaemia In some of these cases it is doubtful whether there was a detailed histological examination Such records of normal kidneys are given by Desmond (1857) who, it is interesting to note, gave his patient a blood transfusion, Fraipont (1914), Shaw (1916, Case 1), Lieven (1920, Case 1), Frankl and Hiess (1921, Case 1), Williams (1925, Case 2) and Ware, Winn and Schelin (1944, Case 2).

ALBUMINURIA AND COLLECTING TUBULE CASTS

Following U.P.A. there is almost always some proteinuria, and this can be identified histologically in the vast majority of cases. The protein may remain in solution in the lumen of the tubules during life, but, after the patient dies, it can be identified in sections as a fine deposit in the lumen due to precipitation [illegible]

third of the patients of the whole series.

The casts in the collecting tubules are seldom seen as early as 8 hours, but are more fully developed from 13 hours onwards In the early cases they are very small, merely forming a thin column in the centre of the tubular lumen. In the later cases they may still be small, or they may have become so large that they occlude all the lumen. They vary in number; sometimes they are found only on careful search, and sometimes every tubule appears to be obstructed The structure is finely granular or fused to a hyaline appearance, similar to the protein casts which are ordinarily seen in nephritis. Though the

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also in other places where the appearances strongly suggest that casts have pressed previously. The flattened epithelium has a heavy eosinophil staining of its cytoplasm, and marked pyknosis and crushing of the nuclei (Fig. 3) In a number of places the epithelium has disappeared as a result of the pressure, so that the cast lies in contact with the basement membrane In later cases there is some regeneration of the epithelium at these sites

In these, as in all pathological conditions where there is occlusion of the lumen or damage to the epithelium of the collecting tubules in the medulla, large monocytes appear in thin vessels in certain parts of the intermediate zone at about 3 to 5 days. During the next few days these cells are gradually replaced by lymphocytes, which form ill-defined foci in the intermediate zone or occasionally in the neighbouring cortex or medulla (Hutchison et al, 1946)

Similar casts are sometimes seen in the distal convoluted tubules in the cortex in the cases which are not developing R C.N They appear first at 8 to 12 hours, as a small shrunken deposit in the lumen of a few tubules. This deposit may increase rapidly, so that in some cases the majority of the distal convoluted tubules contain large solid casts by about 24 hours; other cases may have none whatsoever. There is no direct relationship between the presence of casts in the distal convoluted tubules of the cortex and their presence in the collecting tubules of the medulla; in fact there is often some suggestion that their incidence in the two sites is inversely related

The distal convoluted tubules do not show any characteristic epithelial change, whether they contain casts or not Mallory (1947) has emphasised that, in the early stage of the haemoglobin kidney, these tubules become fatty In any pregnant patient there is usually some lipoid in these tubules, demonstrable more easily by Sudan Black than by the Sudan Reds. It is possible that this lipoid may be increased in amount in toxaemias, though the evidence in support of this is rather slender Similar amounts of lipoid are seen in these tubules in cases of U P.A, but not obviously more than in patients without U P.A There is no discernible relationship between the amount of this lipoid and the occurrence of any of the renal lesions described in this paper The only obvious epithelial change in the present group is a late effect; in Case 11 at 13 days, which had gross albuminuria casts in the collecting tubules, the epithelium of the distal convoluted tubules was excessively nucleated.

The proximal convoluted tubules were dilated in two cases, but were otherwise healthy

To the naked eye, the kidneys of this group may be rather enlarged (mean weight 185 gm.). The cortex is pale and broad, and the medulla sometimes appears congested

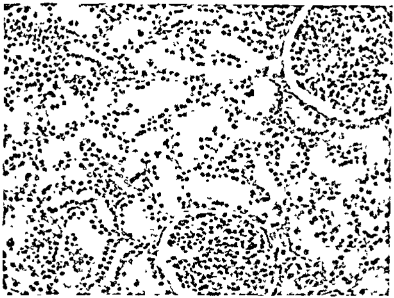


FIG. 1 Renal cortex of "No lesion" type No significant abnormality of glomeruli or tubules 12 hours after U P A.
(All photomicrographs are × 160, except where otherwise stated).

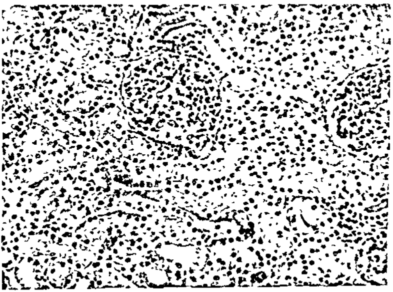


FIG 2 Albuminuria, showing as a protein precipitate in the proximal convoluted tubules 13 hours after U P A

protein casts following U.P.A. are not as coarse as those of haemoglobin origin, they can produce a similar damage to the epithelium of the collecting tubules This epithelium is flattened in places where it is pressed upon by the casts, and also in other places where the appearances strongly suggest that casts have pressed previously. The flattened epithelium has a heavy eosinophil staining [illegible] ...ei (Fig. 3) In [illegible] the pressure, [illegible] In later cases there is some regeneration of the epithelium at these sites

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To the naked eye, the kidneys of this group may be rather enlarged (mean weight 185 gm.). The cortex is pale and broad, and the medulla sometimes appears congested

CASE NOTES

In the entire series of fatal cases, as mentioned above, nearly all the kidneys show albuminuria precipitate in some tubules, and about one-third of them have albuminuria casts in the collecting tubules There are only four cases which show these lesions without any other complicating renal pathology.

The two late cases had massive casts in practically every collecting tubule at some point or other in the medulla. These casts appeared *histologically to be completely occlusive and there was very severe damage* to the lining epithelium of these tubules. Both patients had severe oliguria and renal insufficiency

Case 8. Age 35, para 8, gestation 22 weeks, duration 13 hours. Severe external haemorrhage Delivered at 5 hours. Sudden collapse 5 hours p.p. and died of shock 8 hours p.p

Case 9 Age 18, para 1, gestation 38 weeks, duration 24 hours. Toxaemia for 3 weeks previously Eclampsia, followed 6 hours later by U.P.A.. Eclamptic fits continued to delivery at 15 hours. Died in coma 9 hours p.p.. 600 cc. of urine passed since U.P.A.. Eclamptic lesions in liver.

Case 10. Age 35, para 2, gestation 35 weeks, duration 5 days Toxaemia for 5 days previously. No external haemorrhage. Delivered at 6 hours Became comatose at 2 days, and died in coma 5 days p p. Mean urine output 100 cc. per day. Gross infarction of liver Glucose lesions in kidney.

Case 11. Age 24, para 3, gestation 37 weeks, duration 13 days. Previously had [illegible] minuria Induction, followed by U.P.A. [illegible] a few days, followed by normal volume [illegible] mg. per 100 cc. Died with gross septic endometritis at 13 days p p

LITERATURE

This is considered in detail in Chapter XII.

GLUCOSE KIDNEY

In Cases 10 and 57, which had been treated intravenously with hypertonic glucose solution, many of the proximal convoluted tubules, which had apparently remained healthy previously, developed the gross bloating of epithelial cytoplasm accompanied by pyknosis of the nuclei, which is a characteristic result of this treatment. In the literature there are certain case reports which appear to fall into this category (Batisweiler, 1933, Case 2; Peters, 1945; Govan and MacGillivray, 1950). The lesion is probably analogous to the bullous oedema which occurs in the mucosa of the bladder of patients who have been given this therapy. It is irrelevant to the consideration of renal lesions associated with U.P.A.



FIG 3 Protein casts in collecting tubules of medulla Damage to epithelium around some casts 24 hours after U P A



FIG 4 Hyaline droplets in epithelium of spiral segments of proximal convoluted tubules 12 hours after U P A

HYALINE DROPLET FORMATION

This lesion consists of the presence of hyaline droplets in the epithelium of the proximal convoluted tubules, and particularly in the spiral segments. Occasional proximal convoluted tubules in the cortex are packed with droplets, but many of them are not involved at all

In the mild early lesions, the droplets are small and may be little more than granules In the more advanced cases, they occupy most of the cytoplasm and are large, particularly in the luminal half of the cell (Fig. 4). They are strongly eosinophil but, even in a single cell, they give a very variable reaction with fibrin stains. They do not stain with Sudan. The epithelium is usually swollen, and its mitochondrial zone may show a foaminess which is not due to lipoids. The nuclei invariably remain healthy, and histologically the cells may be judged capable of continued function

This droplet change is first seen in cases at 6 hours, and increases in frequency up to about 18 or 24 hours after the U.P.A.. It seems probable that the droplets may disappear from an individual tubule within a day or two Nevertheless there appears to be some new droplet formation several days later in otherwise normal nephrons around areas of R.C.N.

Hyaline droplet formation is sometimes seen in cases of albuminuria or toxaemia of pregnancy without U.P A.. In the present series there is no clear relation to previous albuminuria, oedema or eclampsia, but the figures are insufficient for valid conclusions

At autopsy, the kidneys of this group are of about normal size (mean wt. 155 gm.) and have a rather pale cortex.

CASE NOTES

This is a common lesion, occurring in about half the cases of the entire series, and it is seen frequently in association with colloid degeneration There are only 3 cases where the condition is not complicated by any other lesion in the kidney

CASE 12. Age 36, para 7, gestation 32 weeks, duration 7 hours. Eclamptic convulsions 10 days a.p and 1 day a.p. Bougie induction External haemorrhage. Delivered at 2 hours Sudden collapse and death 5 hours p p Heart 460 gm

CASE 13 Age 41, para 6, gestation 33 weeks, duration 10 hours Moderate external haemorrhage. Became blind. Died undelivered.

CASE 14. Age 46, para 15, gestation 39 weeks, duration 12 hours. Moderate external haemorrhage. Severe shock. Died undelivered

LITERATURE

Hyaline droplet formation occurs in many types of kidney disease unrelated to pregnancy, and is a complication of most of the renal lesions which are seen after U.P.A . In the literature, the only pure example of hyaline droplet

formation following U.P.A. seems to be that recorded as Case 24 by Ahlstrom (1919) However, the condition is a common one, and there must be many unrecorded cases.

COLLOID DEGENERATION

The term "colloid degeneration" is used here merely as a convenient title for a gamut of lesions which develop in the proximal convoluted tubules. These lesions are sometimes scanty, sometimes extremely extensive The condition appears to develop very quickly after the U.P.A.

At 6 to 12 hours the epithelium of these tubules is usually considerably swollen In the mildest cases, it has a foamy cytoplasm containing a number of small hyaline droplets. In the next grade, the epithelium has a frothy colloid appearance but still contains a few hyaline droplets. The nuclei are pushed to the base of the cell and are usually darkly-staining and misshapen. The luminal margin of the epithelium is indistinct, and the lumen is usually filled by a bubbly glutinous material in which there may be free hyaline droplets (Fig. 5). Those tubules which are more severely affected have an apparent partial disintegration of the epithelial cytoplasm into the lumen, so that the tubule seems to consist of a homogeneous mass of glutinous debris with warped nuclei at its periphery. No droplets are seen in this or the next grade In the most severe lesions, the lumen of the tubule is filled by a colloid material which is partly fused with the epithelium at its periphery. The epithelium is less foamy and is more distinct from the luminal colloid than in the previous grades, its nuclei are more pyknotic

A variant of this epithelial change occurs in the spiral segments It is closely associated with intermediate zone colloid casts, and is more suitably considered in that connection.

In some of the severe cases of colloid degeneration, particularly at about 12 hours, there is a tangle of coarse threads of fibrin filling the lumen of the upper part of the affected proximal convoluted tubules.

At 12 to 24 hours the lesions begin to follow one of two courses In the least damaged tubules, the colloid degeneration begins to regress, and the epithelium probably returns to normal quite soon. It is very difficult to identify the steps of this recovery process, but kidneys, which on other grounds may be presumed to have had colloid degeneration, have normal tubules within two or three days.

In the tubules which were originally more severely damaged, the lesions progress steadily, so that at 24 hours the epithelium has disintegrated to a foamy glutinous debris with fading of its nuclei (Fig. 6). This debris fuses with the similar material in the lumen to form a mass which fills the entire space inside the basement membrane When the original degeneration has been of a particularly colloid type, the final necrotic debris is of correspondingly colloid



FIG 5 Colloid degeneration of proximal convoluted tubules 12 hours after U.P A



FIG 6 Colloid necrosis of proximal convoluted tubules 24 hours after U.P A

appearance. These types of epithelial death are referred to in this paper as colloid necrosis

The later stages of colloid necrosis are not easily distinguishable from those of simple proximal convoluted tubule necrosis. The presence of intermediate zone colloid casts in a kidney is presumptive evidence that the proximal convoluted tubules may have suffered some degree of colloid degeneration or colloid necrosis Some of the later cases in the series show an association of R C.N. with intermediate zone colloid casts. When, as in Case 46, the R C N is of focal or minor degree, there are many areas of cortical parenchyma unaffected by the R C N , and in these it is possible to follow the apparent course of repair of colloid necrosis. In addition, Case 23, which is uncomplicated by R.C N , shows extensive intermediate zone colloid casts and a healing proximal convoluted tubule lesion which is presumably healing colloid necrosis. The following description of the late stages is tentative, as it is based only on these few examples

At about 3 or 4 days, regenerating epithelial cells appear, and spread as a layer between the basement membrane and the debris in the lumen. During the next few days the debris disappears The tubule at 7 days is lined by a flat epithelium very similar to that seen in the repair of proximal convoluted tubule necrosis. The cytoplasm may however be more eosinophil than in that condition, and appears to be nearer in histological character to functional tubular epithelium It is probable that a number of these tubules return finally to near normality, but in other nephrons intertubular fibrosis occurs and the regenerated tubules atrophy

Distribution of the lesions. Colloid degeneration and colloid necrosis are always uneven in severity and extent. In any affected kidney some tubules may show colloid necrosis, others show various types of colloid degeneration, others show hyaline droplet formation, others merely have a little protein in their lumen, and others appear quite healthy. The condition may on the other hand be associated with more severe lesions, either proximal convoluted tubule necrosis or early R.C.N. It is very difficult to delineate with any accuracy the extent of the colloid lesions, because they merge so gradually into the normal areas of the cortex After about 15 hours there are usually complications such as R C N. which further obscure the picture. Despite these difficulties it is possible to make a rough subdivision of the cases as follows:

Cases 16 and 17 show a few small lesions affecting only occasional nephrons scattered anywhere in the outer two-thirds of the cortex The condition is rarely more than a colloid degeneration

Cases 18 and 22 show lesions affecting much larger areas, mainly in the outer two-thirds of the cortex. The juxtamedullary nephrons are not involved, and there are a considerable number of undamaged nephrons near the surface of the kidney and also in broad radial segments of the cortex. In the large

areas of affected cortex, the lesion tends to be of greater severity; many tubules still show only a colloid degeneration, but there are small areas of colloid necrosis mainly localised to small patches in the outer half of the cortex

Cases 15, 19, 20, 21, 23, 36 and 37 show widespread lesions involving most of the outer three-quarters of the cortex and affecting even a few of the juxtamedullary nephrons. The undamaged nephrons are distributed mainly under the renal capsule, in the juxtamedullary region, and in a few narrow radial segments of the cortex. Colloid necrosis of tubules is seen commonly in these cases, either as numerous small foci in the outer two-thirds of the cortex, or sometimes as rather larger areas nearer the surface of the kidney. A few small areas of simple proximal convoluted tubule necrosis are also present in Case 21.

Macroscopically the kidneys with colloid degeneration during the first day are slightly enlarged (mean wt. 170 gm.) and have a pale cortex. The condition later is usually complicated by other lesions.

The case records and the literature on this subject will be discussed at the end of the section on intermediate zone colloid casts.

INTERMEDIATE ZONE COLLOID CASTS

This title describes the accumulation of a peculiar type of colloid filling the entire lumen of almost all tubules which traverse the intermediate zone between the cortex and the medulla (Fig. 7). The colloid has a solid appearance similar to the colloid in thyroid acini (Fig. 8).

This lesion develops remarkably early; it reaches its maximum development usually within 6 hours, and always within 12 hours, after the U.P.A.. However the staining reactions suggest that there are, within this time, two successive depositions of colloid The first is quite solid, is strongly eosinophil, and gives a positive reaction with fibrin stains; it is laid down within the first 6 hours. The second is less eosinophil and usually does not react with fibrin stains; it is deposited at 6 to 12 hours. Neither type gives any reaction for iron.

It is not always easy to identify the individual tubules which are affected in the intermediate zone, because their epithelium undergoes alteration. The epithelium of some spiral tubules and broad ascending limbs of Henle develops a swollen clear cytoplasm resembling that of collecting tubule epithelium Other tubules have considerable flattening of their epithelium by the pressure of the colloid, so that they can only be identified by following them in longitudinal section to their unaffected portions in the cortex or the medulla. Assistance in the identification is provided by the fact that some of the broad ascending limbs of Henle contain golden yellow droplets in the cytoplasm of their epithelium; much more in these cases of U.P.A. than is usually found in other human kidneys. Despite the difficulties, detailed examination shows



FIG 7 Colloid casts (darkly stained) in intermediate zone in a case of extensive R.C.N 9 days after U.P.A (Magnification × 4).

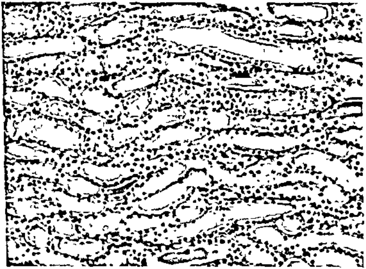


FIG 8 Colloid casts in intermediate zone, filling nearly all tubules 12 hours after U.P.A

quite clearly that the tubules affected are (a) the lower end of the spiral tubule and the upper end of the thin descending limb of Henle, (b) the broad ascending limb of Henle.

This distribution is constant in the condition, and sometimes there are no colloid casts in any other tubules in the kidney. In most cases, however, colloid is deposited in other parts of the nephron. Usually after about 9 hours there are colloid casts throughout the loops of Henle in the medulla. A lesser degree of colloid cast formation is often present in the distal convoluted tubules in the cortex, and, when this is prominent, some deposition of similar casts is usually seen in the collecting tubules in the medulla. Furthermore, in about half the cases there is a deposition of the same colloid material in the capsular space of a few glomeruli. This is variable in amount but may be so great that it distends the capsule, though the glomerular tuft always appears normal. The colloid from the capsular space may extend into the first few loops of the proximal convoluted tubule, but it does not continue into the lower loops and, in particular, not into the spiral segments

In consistency the colloid varies somewhat from place to place In the thin descending limbs and the broad ascending limbs of Henle in the intermediate zone, in the loops of Henle in the medulla, and in the distal convoluted tubules in the cortex, it appears very solid, though it may have some marginal scalloping. In the upper part of the spiral tubules the colloid is very frothy and rather weakly staining Further down this segment it becomes more solid, though with bubbles around its periphery, and at the lower end of the segment it is solid throughout. The colloid in the glomerular capsules is sometimes diffusely vacuolated but, in the cases where the whole capsule is distended, it is a completely solid gel. In the upper loops of the proximal convoluted tubules it is always foamy

Some of the changes in the epithelium of the affected tubules have already been mentioned. The epithelium of the broad ascending limbs of Henle may be flattened, but its nuclei are normal The spiral tubules show a transient foaminess of the cytoplasm with hyperchromatism and warping of nuclei; this disappears by 24 hours although the colloid still remains in the lumen. The upper loops of the proximal convoluted tubules which communicate with colloid-filled glomerular capsules usually show heavy deposition of hyaline droplets in their cytoplasm from about 12 hours onwards. These hyaline droplets may also be seen in the spiral tubules which lie in the medullary rays.

There is no increase in the amount of cast formation after 12 hours. The [illegible] the intermediate zone [illegible] hey [illegible] ion

they are remarkably non-irritant; the tubular epithelium regains its healthy appearance quite soon, and there is no local infiltration of inflammatory cells.

In cases without R C.N., intermediate zone colloid casts are associated invariably with some degree of colloid degeneration or colloid necrosis of proximal convoluted tubules, though there is no quantitative relationship between these conditions The colloid casts are not found in association with albuminuria casts in collecting tubules, or with simple necrosis of proximal convoluted tubules, but they are seen in about one-third of the cases of R C N.. There is no relationship between the amount of colloid cast formation in the intermediate zone and the severity of the R.C N , which may vary in extent from focal to gross. It is important to point out that in cases of gross R C N., where practically the whole cortex is destroyed, nearly every tubule in the intermediate zone may be plugged by colloid casts without any trace of such casts in cortical tubules in the necrosed area.

Macroscopically the presence of these colloid casts can be recognised in some cases by a translucent brown appearance of the intermediate zone

CASE NOTES

As has been indicated above, colloid degeneration of proximal convoluted tubules is nearly always associated with intermediate zone colloid casts. In the present series there are 9 cases which show both these conditions without the complication of any other lesions These cases are usually of less duration than 24 hours Most of the cases with the colloid casts which are observed in the later puerperium have an associated R.C.N

CASE 15 Age 20, para 3, gestation 34 weeks, duration 6 hours. Delivered at 2 hours Severe atonic p p h Died 4 hours p p

CASE 16. Age 29, para 4, gestation 40 weeks, duration 9 hours. U P A during spontaneous labour Delivered at 4 hours. Atonic p p h Died 5 hours p p

CASE 17 Age 38, para 7, gestation 30 weeks, duration 9 hours Toxaemia for 2 weeks previously U P A during premature labour. Moderate p.p h. Died 4 hours p.p Eclamptic lesions in liver.

CASE 18 Age 44, para 15, gestation 28 weeks, duration 10 hours Severe external haemorrhage. Delivered at 9 hours. Died 1 hour p.p. Heart 390 gm

CASE 19 Age 41, para 2, gestation 32 weeks, duration 12 hours. Toxaemia for 2 months previously. Delivered at 11 hours. Some p p h Died 1 hour p.p. Heart 430 gm. Eclamptic lesions in liver.

CASE 20 Age 30, para 2, gestation 32 weeks, duration 12 hours. Toxaemia for 1 week previously. Severe external haemorrhage and became blind Died undelivered. Eclamptic lesions in liver

CASE 21 Age 41, para 12, gestation 38 weeks, duration 12 hours. No external haemorrhage Severe shock Died undelivered Heart 500 gm.

CASE 22 Age 41, para 4, gestation 36 weeks, duration 15 hours. Severe external haemorrhage and much shock. Died undelivered

CASE 23 Age 36, para 2, gestation 30 weeks, duration 7 days. Toxaemia for 1 week previously. U P.A. during labour. Oliguria during puerperium, improving to 800 cc. on last day. Terminal sudden collapse

LITERATURE

In the literature on U.P.A. there are a number of tubular lesions recorded which might be descriptions of colloid degeneration or colloid casts, but the details are usually inadequate for any definite conclusions. Among these records may be mentioned Bar and Kervily (1906), Louros (1926, Case 1), Batisweiler (1933, Case 2), Fauvet (1934, Case 1), de Snoo (1936, Case 2), and Young (1942 b, Case 1).

White (1919) reported, as Case S.O., a 2 para who had induction at 27 weeks for albuminuria, and developed puerperal oliguria. He performed a renal biopsy on the 17th day of the puerperium and has kindly allowed us to examine his histological slide and to report from it. This showed two conditions The distal convoluted tubules in the cortex were dilated and their lumen was filled with typical colloid casts; the intermediate zone was not included in the biopsy. In a few of these tubules there was a little proliferation of epithelium into the surface of the casts. In numerous small areas, the proximal convoluted tubules were in a condition of advanced regeneration corresponding to about 17 days; many of these tubules were atrophic and were separated by interstitial fibrosis. The spiral segments had a peculiar development of club-shaped processes of their luminal surface, very similar to what is seen in apocrine glands, and their cytoplasm contained many fine hyaline droplets. This case is interpreted here as the late stage of a kidney which had had (a) extensive colloid degeneration, now recovered, (b) small areas of colloid necrosis, now healed, and (c) numerous colloid casts, showing the early stage of their removal.

PROXIMAL CONVOLUTED TUBULE NECROSIS

The condition to be described under this heading is a necrosis, of the type *traditionally called "coagulative" necrosis, which involves the proximal* convoluted tubules including their spiral segments. There is no associated damage to the distal convoluted or collecting tubules.

The terminology used here requires a little explanation. The word necrosis implies two distinct steps (a) the death of the cell, (b) the subsequent structural changes in the dead cell. These structural changes are referred to in this paper as "necrosis-changes". It is only when they have occurred, that necrosis is histologically recognisable; before they have occurred, the dead cell retains the appearances it had when it was alive, and the word "necrosis" is not applied to it. The necrosis-changes progress rather quickly for a day or two and then more slowly; the rate of their development varies under the influence of a number of factors which will be considered in detail in Chapter XI.

The following description is based primarily on the cases of the present group. Further information has however been obtained from the groups of

R.C.N. to be described subsequently; in such cases there are usually some areas of pure proximal convoluted tubule necrosis at a distance from the lesions of R.C.N. The present description does not include any tubular lesions in areas which are considered to be probably the early stage of R.C.N.

EARLY STAGES

At about 6 *hours* early necrosis can be seen in the neck and the first two or three loops of the proximal convoluted tubules of a few nephrons (Fig. 9). The mitochondrial zone of the epithelium becomes highly eosinophil, dense and slightly granular, while all the luminal part of the cytoplasm becomes foamy and weakly staining. The nuclei show hyperchromatism and then shrink quite evenly to small round or oval masses. The epithelium of the tubule becomes slightly separated as a continuous loose sleeve inside the basement membrane. This sleeve-separation is characteristic, and is presumably due to a stripping-up of the epithelium by fluid, which may well be glomerular filtrate. It is not an artefact. Firstly, it is observed in kidneys removed without any handling at all, and fixed in various ways within 20 minutes after the death of the patient. Secondly, in cases of early R.C.N. a glomerulus may bleed into such a necrosed tubule, and the red corpuscles are then seen not only in the lumen but also between the sleeve of necrosed epithelium and the basement membrane. Thirdly, this sleeve-separation becomes a more prominent feature in the later cases, and can still be observed in the special case of R.C.N. as late as 8 or 10 days.

The remainder of the proximal convoluted tubules, even those in immediate contact with necrosed tubules, show as yet no recognisable histological abnormality. In particular, their nuclei remain leptochromatic and there is no evidence of colloid degeneration. Nevertheless, as will be explained in the discussion, these apparently normal tubules may in fact be dead; the absence of cytological alteration in them being merely due to the fact that necrosis-changes have not occurred.

At 12 *hours* the eosinophil band of the mitochondrial zone appears more condensed, and the foamy luminal half of the cell is disintegrating and disappearing. The nuclei are still deeply pyknotic. The separation of the epithelium as a continuous sleeve is much more prominent, and this sleeve often shows radial fractures at one or two points on its circumference (Fig. 10).

The necrosis tends, at this stage, to become more extensive in two ways; more loops of the affected nephrons are necrosed, and the necrosis affects a greater number of nephrons, though still in a patchy manner.

The spiral segments usually show some pyknosis and warping of their nuclei, which are pushed to the base of the cell; their cytoplasm is foamy and granular [illegible] segment, leaving some inter- [illegible] There are no colloid casts in



FIG. 9 Early necrosis and sleeve-separation of the neck and upper loops of a proximal convoluted tubule. 8 hours after U P A



FIG 10. Further extension of proximal convoluted tubule necrosis. Slight radial fractures of separated sleeve of epithelium. 12 hours after U.P A

At 24 hours the main difference is in the much greater extent of the lesions. Most of the proximal convoluted tubules are affected along their whole length, and show considerable sleeve-separation. The nuclei are deeply pyknotic or are fading In addition, some tubules show necrosis of epithelium which is of normal height and has not passed through the stage of dense eosinophil staining of the mitochondrial zone.

At this time most of the tubules have reached the same stage of necrosis, and the lack of uniformity which was seen in some of the earlier cases is now less evident. Nevertheless it is nearly always possible to find, in the necrosed loops, isolated cells or occasional small groups of cells which remain alive and firmly attached to the basement membrane. Some of these remain healthy, and are destined to be the source of the subsequent repair of the tubule. Other isolated cells which have survived to this time develop a diffuse granularity at 24 hours and show necrosis-changes shortly afterwards, but they remain attached to the basement membrane.

The spiral tubules appear much the same as at 12 hours

At 36 hours the majority of the tubules are necrosed and have lost their nuclei (Fig 11). In some tubules the loose sleeve of necrosed epithelium is still present, the fractures are more obvious. In other tubules the fragments of the sleeve have disappeared, leaving only a naked basement membrane around an empty lumen. The tubules whose epithelium has necrosed without passing through the stage of condensation of the cytoplasm are now represented by a mass of granular debris

Many of the loops which lie under the renal capsule undergo the full process of necrosis, but not uncommonly the epithelium becomes necrosed on the deeper side of the loop and survives on the side which is in direct contact with the renal capsule This surviving part of the epithelium becomes very fatty within 2 days, and this appearance remains for at least 10 days.

The interstitial tissue between the necrosed tubules appears normal at this time, and there is no infiltration of inflammatory cells Nevertheless, fat stains show small patches where there is a fine deposit of lipoid in the intertubular interstitial tissue and in the base of the epithelial cells around them. It is difficult to ascertain, in frozen sections, whether the deposit is in relation to dead or live tubules

[illegible]

other places the epithelium forms a granular necrotic mass which occludes the lumen There is never any formation of continuous sleeves of dead epithelium in these tubules. As far as can be judged from their situation and number, the spiral tubules which become necrosed seem to be those of nephrons whose proximal convoluted tubules are necrosed.

Distribution of the lesions. The extent and distribution of this proximal convoluted tubule necrosis is variable and, as indicated previously, may be difficult to assess in the early cases. The pattern is much the same as that of colloid degeneration:

(a) When there are only a few small lesions, these involve occasional nephrons scattered anywhere in the outer two-thirds of the cortex. The lesions may easily be missed in early cases unless the sections are studied carefully. (Cases 24, 25, 26 and 30)

(b) Sometimes there are lesions involving small groups of nephrons in various parts of the cortex, but in general not affecting those near the surface of the kidney or near the medulla. (Cases 27, 28 and 31)

(c) More widespread lesions may occur, distributed in large patches throughout most of the outer two-thirds of the cortex, and affecting some nephrons directly under the surface of the kidney. (Case 32)

(d) Very extensive lesions are sometimes seen. These destroy almost all the nephrons in the outer three-quarters of the cortex. The unaffected nephrons lie in patches under the renal capsule, in the juxtamedullary region, and in a few radial segments of the cortex. (Cases 29 and 33)

REPAIR STAGES FROM 2½ TO 7 DAYS

Proximal convoluted tubules. The first signs of repair are seen in very occasional tubules at 66 to 72 hours A flat sheet of basophil cytoplasm spreads over the surface of the denuded basement membrane. This cytoplasm contains a few nuclei, which may be in mitosis. As mentioned above, this new epithelium probably originates from the isolated epithelial cells which have survived in the otherwise necrotic tubules.

At 4 days extensive healing is in progress, and most of the tubules are relined by a very thin basophil epithelium The lumen may be filled by granular debris, or may contain the remains of the sleeve of necrosed epithelium, or may be quite empty; this depends on the different forms that were taken by the necrosis in its development. The new epithelium nearly always spreads between the basement membrane and the debris, but occasionally, when the debris is pressed against the side of the tubule, the regenerating epithelium climbs as a layer over the surface of the mass. In this way, large or small fragments of the debris may be included in the new epithelium. In the special case of the isolated cells which had remained alive for the first day but had subsequently died, the remains of these cells can be identified as large round eosinophil masses engulfed in the new epithelium.

Some of the regenerating cells become rounded-off and desquamated into the lumen of the tubule. These cells may contain the eosinophil masses just described, or their cytoplasm may be pale and rather fatty or foamy. Their nuclei are sometimes lobulated or double.

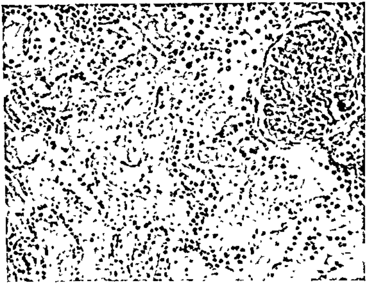


FIG 11 Fully developed proximal convoluted tubule necrosis 36 hours after U P.A.



FIG 12 Repair of necrosed proximal convoluted tubules by flat regenerating epithelium 4½ days after U P A

By the 5th day every proximal convoluted tubule has been relined in this manner (Fig. 12). The new epithelium slowly becomes more neutrophil and thicker, so that by the 7th day it has reached a low cuboidal form. During the same period the remaining debris is removed, and at 7 days most of the tubules have an empty lumen, though some of them still contain cells which have rounded-off and become desquamated.

At 3 to 4 days a little oedema is evident between the regenerating tubules, and the interstitial cells have unusually large nuclei and appear to be more numerous than is normal. During the period from the 4th to the 7th day the intertubular oedema becomes greater, but the endothelial cells return to normal in number and appearance However by the 6th or 7th day a few small monocytes have appeared, and there are occasional fusiform nuclei suggesting fibroblasts.

Spiral segments Despite the relatively large number of live cells remaining in the spiral segments, regeneration begins there a little later than in the upper loops of the proximal convoluted tubules. The early stages of this repair are seen in very occasional spiral segments at 4 days. A thin sheet of basophil cytoplasm creeps between the basement membrane and the debris in the lumen, and by about the 6th day almost every spiral segment has been relined, though the new epithelium remains very thin.

The interstitial tissue between these regenerating spiral segments never shows any oedema, cellular infiltration or other reaction.

LATER STAGES

The development of the lesion has been studied up to 13 days, but not later. During this period the regenerated proximal convoluted tubules follow one of two courses:

(a) In some patches, the tubules remain of good size, and their epithelium becomes more eosinophil though not yet of normal thickness. The interstitial tissue between them is still oedematous and rather fibrillary at 10 days, but the oedema is less at 13 days A few small monocytes are present between the tubules at 10 days, and can still be seen at 13 days (Fig. 13). Presumably, a number of these regenerated tubules finally return to normal structure and function.

(b) In other patches, many of the regenerated tubules begin to atrophy and disappear. This is evidenced at 10 days by a reduction in size of these tubules, some of which are represented only by small groups of cells. At 13 days there are few or no regenerated tubules remaining in these areas; the interstitial tissue here is excessive and shows, not only a coarse fibrillary appearance, but also what appears to be a true fibroblastic reaction (Fig. 14).

It is not easy to identify regenerated spiral segments during this late phase, and their position in the kidney provides the main clue for their recognition.



Fig. 13 Interstitial fibrillary oedema [illegible] convoluted tubules 12 days after U.P.A.



Fig. 14 Area of complete loss of necrosed [illegible] Some distal convoluted and collecting t[illegible] fibroblastic reaction of stroma 12 days [illegible]

. No external

U.P.A. during p.p. Toxaemia for One eclamptic

Oedema for 4½ Bilateral supra-

Some external den collapse and

[illegible]e of proximal [illegible]ble information [illegible]er there is true of post-mortem [C]ases 3, 4 and 5), [C]ase 3), Fordyce Willson (1922), [illegible]se recorded by [illegible]s

[illegible]mary proximal [illegible]h which have [illegible]sel, i.e. in the termination [illegible]llaries arise. been seen in [illegible]ular thrombi [illegible]rs earlier At [illegible]ibrin strands [illegible]ter, but other- [illegible] presumably it [illegible]ways appears in [illegible]t adh[illegible] to th[illegible] [illegible]ally a[illegible] Th[illegible] [illegible]re no [illegible] [illegible], this [illegible]ure

The epithelium is of cuboidal type and is only weakly eosinophil; the nuclei are in excessive numbers and still show some mitoses. The interstitial tissue between these regenerated spiral segments does not show any significant change.

Macroscopic appearances. During the first day, the kidney is of about normal size (mean weight 160 gm) and has a rather pale cortex (Fig. 15). From 2 days onwards, the cortex is broad and pale, and the mean weight of each kidney is 185 gm. (Fig. 16).



FIG 15 Kidney involved by early proximal convoluted tubule necrosis No macroscopic abnormality 14 hours after U.P A (½ natural size)



FIG 16 Kidney showing later stage of proximal convoluted tubule necrosis The cortex is broad and pale as a result of interstitial oedema 4½ days after U.P.A (½ natural size)

CASE NOTES

There are 10 cases in the present series which show an uncomplicated necrosis of the proximal convoluted tubules

CASE 24 Age 35, para 4, gestation 40 weeks, duration 5 hours. No external haemorrhage Delivered at 4 hours Severe p p h. Died 1 hour p.p

CASE 25. Age 34, para 8, gestation 32 weeks, duration 7 hours. Very severe external haemorrhage. Died undelivered.

CASE 26. Age 42, para 13, gestation 40 weeks, duration 7 hours. Toxaemia for 2 months previously. Severe external haemorrhage Delivered at 6 hours. Died 1 hour p.p. Anuria from U.P.A. to death Heart 450 gm Eclamptic lesions in liver.

CASE 27 Age 36, para 9, gestation 40 weeks, duration 8 hours Pre-eclampsia 1 day previously No external haemorrhage. Died undelivered. Anuria from U.P.A. to death.

CASE 28 Age 33, para 5, gestation 30 weeks, duration 10 hours. Toxaemia for 2 months previously. Slight external haemorrhage. Delivered at 4 hours. Severe shock. Died 6 hours p p.

CASE 29 Age 46, para 15, gestation 40 weeks, duration 12 hours No external haemorrhage. Severe shock. Died undelivered. Heart 480 gm.

CASE 30 Age 27, para 3, gestation 36 weeks, duration 14 hours. U.P.A. during labour. Delivered at 4 hours. Sudden collapse and death 10 hours p p

CASE 31. Age 23, para 1, gestation 35 weeks, duration 22 hours. Toxaemia for 1 month previously. Vomiting followed U.P.A. Delivered at 20 hours One eclamptic convulsion, and death 2 hours p.p.

CASE 32 Age 39, para 12, gestation 40 weeks, duration 36 hours Oedema for 4½ months previously Induction Sudden collapse 7 hours p p. and died Bilateral suprarenal necrosis.

CASE 33 Age 32, para 5, gestation 30 weeks, duration 4½ days Some external *haemorrhage. Delivered at 12 hours Oliguria in puerperium* Sudden collapse and death 4 days p p.

LITERATURE

In the literature there are many descriptions suggestive of proximal convoluted tubule necrosis following U P.A., but very little reliable information. It is often impossible to distinguish from the accounts whether there is true

e of post-mortem

Cases 3, 4 and 5),

Case 3), Fordyce

and Johnstone (1921), Ley (1921, Cases A1, A2 and 3), Willson (1922), Williams (1925, Case 1), and Batizfalvy (1937, Case 1) One case recorded by Batizfalvy (1937, Case 7) may be a healing tubular necrosis

BENIGN GLOMERULAR THROMBOSIS

As a further development in kidneys which are the seat of ordinary proximal convoluted tubule necrosis, there may be a number of glomeruli which have small loose thrombi in their capillaries or in the stalk afferent vessel, i e in the blood vessel in the trunk of the glomerular tuft which forms the termination of the afferent arteriole, and from which the glomerular capillaries arise.

The thrombi in the glomerular capillaries have not actually been seen in this condition before 14 hours but, from the time of origin of similar thrombi

must be attached to the endothelium at some point, it always appears in sections to be quite free in the centre of the lumen and not adherent to the

moderately dilated. The thrombus has the same structure as the capillary

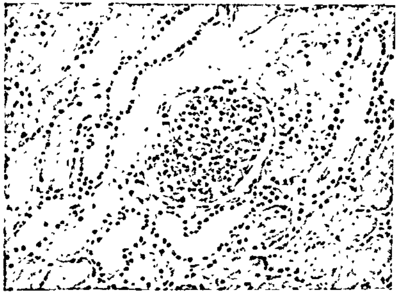


Fig 17 Benign glomerular thrombosis affecting only one capillary loop The proximal convoluted tubules are necrosed, but the glomerulus and the distal convoluted tubules remain alive 2 days after U P A



Fig. 18 Benign glomerular thrombosis involving the stalk afferent vessel. There is much necrosis of proximal convoluted tubules but not of distal convoluted tubules 3 days after U.P.A.

thrombi, and forms at about the same time. It lies quite free in the lumen, as if it had been moulded there and had then shrunk to about two-thirds of its original size (Fig. 18). It has a smooth clove-shaped outline with a rounded narrow proximal end where it reaches into the afferent arteriole, and a bulbous upper end which sometimes bifurcates a short distance into the capillary loops. The endothelium of the stalk afferent vessel is normal, and the entire glomerular tuft is healthy. The thrombus remains unchanged for at least 12 days and excites no reaction during that time, either in the stalk afferent vessel or in the glomerulus.

This benign glomerular thrombosis is not associated with any necrosis of glomeruli, interstitial tissue or distal convoluted tubules It is harmless in itself because it does not obstruct the vessels, but it must be considered as related to the more severe thrombosis which is seen in the focal varieties of R.C N , and which occludes the stalk afferent vessel in dead glomeruli.

Benign glomerular thrombosis forms a link between simple proximal convoluted tubule necrosis and R C.N . If a kidney shows extensive proximal convoluted tubule necrosis with benign glomerular thrombosis, a careful search will almost always reveal some small areas of R.C.N. elsewhere in the kidney In the present series there are several cases of R.C N. in which benign glom[illegible] of the cortex, but there are [illegible] thrombosis, although ther[illegible]

In the literature, there are numerous descriptions of thrombosis in glomeruli, nearly always in association with R.C.N.. It does not appear however that any clear differentiation has been made between this benign glomerular thrombosis and the more severe glomerular thrombosis which will be described in the next Chapter.

CHAPTER V

THE EARLY STAGES OF RENAL CORTICAL NECROSIS

The early stages of R.C.N. are in some ways not very easy to distinguish from the early stages of widespread proximal convoluted tubule necrosis. At this stage the areas which are destined to become completely necrosed are not clearly outlined but they can be recognised by various criteria; these have been established by following three lines of evidence, each of which leads to the same conclusions.

(1) In certain of the groups of R.C.N., the cases are at such time intervals that it is possible to trace back a clear histological series of changes from the latest to the earliest cases of the group. In other groups of R.C.N., there are insufficient intermediate cases to establish all the steps of the series, but there is an obvious agreement between those steps which are represented and the corresponding steps in the other groups.

(2) In advanced R.C.N., the renal parenchyma in the centre dead areas undergoes only a very slow type of necrosis-change, and thus remains "fixed" with the same pattern that it had in its early stages. All the steps in the development of this pattern can be observed in the series of cases which are classed as early R.C.N.

(3) One case of the present series (Case 64) was examined by biopsy at 36 hours after the U.P.A.. This is of importance for two reasons: (a) it shows the 36 hour stage of a kidney which at autopsy at 8½ days was found to have gross R.C N (the earliest biopsy recorded in the previous literature on R.C N. was at 55 hours); (b) it shows the intermediate stage between the 4 autopsy cases at 22 to 27 hours (Cases 36, 37, 39 and 41) and the 3 autopsy cases at 48 hours (Cases 48, 59 and 60).

At the operation there was a slightly blood-tinged oedema of the perirenal tissue. Externally the surface of the kidney appeared damson-coloured. When the kidney was incised, there was no bleeding at all until the incision reached to about the intermediate zone, when bright arterial blood appeared. The specimen of cortex removed showed a rather streaky appearance of dull red areas about 1 mm. in diameter on a damson-coloured background (Fig. 19). This same kidney at autopsy showed the classical picture of gross R.C N., the cortex being opaque white with a congested juxtamedullary margin and patchy areas of subcapsular congestion (Fig. 20).

Histologically the biopsy specimen showed (a) the fully developed stage of those features on which the examples of early R.C.N. in the present series have been differentiated from less severe lesions, (b) the early stages of the

arterial thrombosis and of the other lesions which are fully developed in the later cases. The histological appearances will be described in the appropriate parts of the next two Chapters.

The very deep purple colour of this R C.N. kidney at 36 hours is in striking contrast to the pale pink kidney observed in a decapsulation (without biopsy) at 36 hours by Groen and Lindeboom (1940) It seems probable that the renal lesion in their case was mainly a necrosis of proximal convoluted tubules, though there was presumably a scanty focal R.C.N in addition.



FIG 19 Biopsy of renal cortex in gross R.C N 36 hours after U P A (Magnification × 4)



FIG. 20 Renal cortex at autopsy in same case as Fig. 19 8½ days after U P A (Magnification × 4)

DETAILS OF STAGES UP TO 36 HOURS

The following description of the course of the changes is a general one which is applicable to all cases of early R C N.. The extent of the early changes is of course variable; the early cases of focal R C.N show correspondingly small lesions, whereas the early cases of gross R.C.N. show the widespread distribution of the lesion at this stage.

8 to 12 hours. The first recognisable stages of R.C.N. can be seen in Cases 42 and 43, at 8 and 12 hours respectively after the U.P.A.. Throughout large ill-defined areas, the epithelium of all the proximal convoluted tubules has small, round and very dark nuclei. Some of these tubules have epithelium of normal height, but loosened slightly from the basement membrane. Other tubules show the early stages of a necrosis, which has as yet advanced only to the stage of eosinophil cytoplasm and small fading crumpled nuclei, with a little sleeve-separation of the dead epithelium in a varying number of loops (Fig. 21). The spiral tubules show some pyknosis of their nuclei, and their cells tend to split away from one another though remaining still attached to the basement membrane. A few of the distal convoluted tubules have some loosening of their epithelium, with an eosinophil or foamy cytoplasm and darkening of occasional nuclei. This change is of considerable importance because it is not seen in the cases classified as simple proximal convoluted tubule necrosis

Some of the [illegible] free in their capillary [illegible] thrombosis. Th[illegible] 27 hours, though the thrombi are sometimes scanty and hard to find. There is *no dilatation or congestion of the capillary loops, and no alteration of their* endothelial nuclei. Some of these capillaries contain a few red corpuscles, but no more than are seen in sections of normal kidneys. The stalk afferent vessels are not dilated or thrombosed. Occasional fibrin thrombi are present in the intertubular capillaries, but the interstitial tissue appears otherwise normal. The arteries look quite healthy; they sometimes contain a little blood which stains normally.

14 to 18 hours. At this period the pyknosis of nuclei in the proximal convoluted tubules is more marked, but the necrosis-changes are clearly lagging behind what would be seen in a case of simple proximal convoluted tubule necrosis. The epithelial cells of the distal convoluted tubules usually show disintegration of the cytoplasm at their cell boundaries, though the nuclei and perinuclear cytoplasm remain; this gives rise to dissociation of the cells from each other. These tubular changes may be almost universal throughout the cortex, as in the early stages of gross R.C.N., or they may affect smaller areas, as in the less severe types of R.C.N.

The small thrombi are still present in some glomerular and intertubular capillaries. In addition, certain of the glomeruli have moderate dilatation of the stalk afferent vessel with a fine dusting of fat in its wall. In the early cases of extensive R.C.N. this vessel remains empty, but in the cases of minor or focal R.C.N. it may be occluded by a thrombus similar in structure to the benign thrombosis which has been described earlier. In these cases of early R C.N., however, the thrombus occludes the lumen and is adherent to the walls of the vessel (Fig. 22). Occasionally it has a small rat-tail prolongation

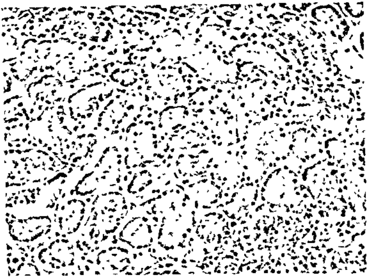


FIG 21 Early stage of gross R C N showing widespread pyknosis in proximal convoluted tubules 12 hours after U P A.



FIG. 22. Solid occlusive thrombi in stalk afferent vessels of glomeruli in early focal R C N The distal convoluted tubules remain alive 3 days after U P A

for a short distance down the centre of the lumen of the afferent arteriole. Small groups of glomeruli show congestion of their tufts; this particular lesion is more obvious at 22 to 27 hours, and will be described under that heading.

In some of these cases, individual small intralobular arteries and their branches are dilated, and fine droplets of fat are present in their media. Usually the lumen is empty or contains a little blood, but occasionally, in what appear to be early cases of minor R.C.N., these small arteries may be occluded by a finely granular solid thrombus. The interstitial tissue shows no significant changes

22 *to* 27 *hours* The proximal convoluted tubules show little or no difference from the earlier appearances; in particular, the necrosis-changes in individual nephrons have not progressed, and are usually arrested at an early stage of their development The spiral segments show breaking-up of their epithelium into large polyhedral cells which lie free in the lumen of the tubule. These spiral tubules with dissociated epithelium are easily distinguishable from distal convoluted tubules with dissociated epithelium, because the cells of the former are of larger size and have poorly staining nuclei

In many places, groups of glomeruli show considerable congestion, which is interpreted here as indicative of stasis. This lesion is first seen at about 14 *to 18 hours and there is no evidence, in the present series of cases of R.C N.* following U.P.A , that it begins in any glomeruli later than 27 hours. The [illegible] capillaries are distended with [illegible] re powdered with fine lipoid [illegible] 14 to 18 hours, and are flattened to thin crescents by about 22 hours. Usually the whole tuft is congested, sometimes so much that it is herniated into the tubule, but occasionally only two or three capillary loops are involved. The packed red corpuscles may extend through the efferent arteriole into the neighbouring intertubular capillaries, which then have an appearance of haemorrhage or great congestion. Fibrin thrombi may also be seen in some of the capillary loops, in the stalk afferent vessels, and in occasional efferent arterioles There is no clear relationship between the stasis-congestion of glomeruli and this thrombosis; the two conditions may occur together or independently of each other.

This stasis lesion is an important one, but the identification of its very early *stages may be difficult The histological problem is to differentiate* between (a) a congested but living tuft in which the circulation may be very slow, or may have become temporarily arrested but will subsequently open up again, and (b) a congested dead tuft where the bloodflow is permanently arrested. The former type occurs at a later stage in the zone of partial survival. The identification of the true stasis glomerulus (type b) in the early stages of R.C N. depends upon certain lines of evidence. Firstly, the glomerular endothelium is dead and quite soon develops the characteristic flattening of its nuclei; a

about 12 to 20 hours later, show dehaemoglobinisation of the red corpuscles in the stasis-tufts; as will be explained in the next section, this indicates that the blood in these tufts has been stationary for about 12 to 20 hours There are thus good grounds for believing that, in the corresponding early cases, many if not all of the glomeruli which appear congested are in fact in a condition of permanent stasis

Sometimes the congested glomerulus bleeds into its proximal convoluted tubule, filling three or four of the upper loops with a mass of red corpuscles. In the absence of such haemorrhage, there is usually little or no evidence of exudation from the tuft; neither protein deposit nor colloid is seen in the capsular space.

In some cases a few of the arterioles are moderately dilated but the arteries show no lesions. In other cases many of the arteries and arterioles are dilated at 22 to 27 hours, so that they become very prominent in histological sections, in contrast to what is seen in the normal kidney. Their walls show a variety of changes The internal elastic lamina is stretched flat and may be fractured in a few places In the media, the muscle cells have obvious pyknosis of their nuclei and a shrinkage of their cytoplasm, both longitudinally and laterally, to a thin but densely eosinophil band lying widely separated from its collagenous framework. (In cross section, these muscle fibres may be difficult to differentiate from red corpuscles) Fine droplets of fat are usually present in these cells A few arteries appear to have lost their media entirely in small areas or even in long segments, and their wall is represented only by the internal elastic lamina and the adventitia, with a space between them. This space may be empty, or it may contain scattered globules of fat or some fibrin or a few polymorphs, or it may be packed with red corpuscles (Fig 24). Any remaining muscle nuclei are so warped that they can easily be confused with polymorphs. In general these lesions are more prominent in small arteries, and may occur in them earlier than 22 hours The larger vessels rarely have red corpuscles in their media, though they undergo full necrosis.

When occasional small intralobular arteries have been occluded by solid thrombus in cases of minor R C N., the related afferent arterioles may contain a looser thrombus which extends up into the stalk afferent vessel. On the other hand, in cases which show the incipient stages of patchy or gross R C N., the arteries and arterioles are not thrombosed They may contain a little blood in their lumen, but there is no packing together of the red corpuscles

The intertubular capillaries now show much pyknosis of their nuclei. Some of them contain the small fibrin thrombi previously mentioned There is no significant infiltration of polymorphs between the damaged tubules.



Fig 23 Glomerular stasis in early patchy R C N 27 hours after U P A

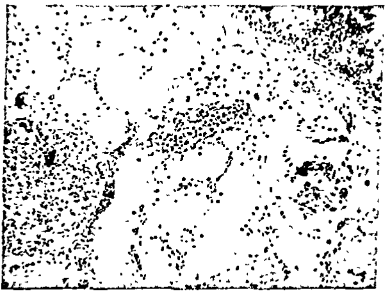


Fig 24. Necrosis of small artery with replacement of its media by red corpuscles, in early minor R.C N.. 22 hours after U.P.A.

DEHAEMOGLOBINISATION

Towards the end of this period the red corpuscles in certain areas begin to lose their haemoglobin, though their outline remains unchanged From experimental and other evidence, it may be stated at this point that dehaemoglobinisation occurs whenever red corpuscles remain stationary in an area of ischaemic parenchyma. This process develops in the course of about 10 or 12 hours after the cessation of the bloodflow. The dehaemoglobinised corpuscles retain their outline for about a further 10 hours, and then disintegrate rather rapidly into a trivial amount of fine debris

Dehaemoglobinisation of stationary red corpuscles is a much slower process in tissues where there is a continuing blood supply For example, the subperitoneal haemorrhages over the uterus in cases of U.P.A. show quite well-staining red corpuscles when the patient dies several days after the haemorrhage occurred.

The process described here is apparently the same as that which leads to the disappearance of all red corpuscles in a simple infarct of the kidney more than one day old (Ribbert, 1899). It may be simulated by artefacts due to fixation or by post-mortem autolysis, and consequently care must be taken in the histological diagnosis

REMAINDER OF THE CORTEX

As has been explained, it is difficult to determine at 12 hours which parts of the cortex are involved by incipient R.C N and which parts have only lesser damage A more definite opinion can be formed at 24 hours, and by 2 days the differentiation is clear.

The parts of the cortex which are not involved by R C N show healthy distal convoluted tubules, and the nuclei of the interstitial tissue remain apparently normal, but the proximal convoluted tubules in these areas are [illegible]

tubules show hyaline droplet formation. The juxtamedullary nephrons may be involved by these lesions but, not infrequently, they show only a simple albuminuria precipitate in the lumen of their tubules.

Colloid casts in the intermediate zone are present in some of the cases at quite an early stage, albuminuria casts in collecting tubules in the medulla may be seen, particularly at 24 hours or later.

CASE NOTES OF EARLY R.C.N

The following cases of early R.C.N., from 8 to 27 hours after the U.P.A., have been observed in the present series. They are classified here according

to the apparent extent of the R.C.N. which was developing; this classification cannot be of a high degree of accuracy in the early stages of the lesion, but probably gives a fairly true picture of the condition. The cases recorded as focal and as minor R.C N had lesions in the stalk afferent vessels and small arteries respectively; this is in agreement with the findings in the later cases of these grades. The cases recorded as patchy and as gross R.C N. showed much less developed lesions and had not yet reached the stage of arterial thrombosis.

It may be mentioned at this point that the lesions recorded here as representative of early R.C.N. are in many ways similar to those of confluent focal R.C.N . This latter condition, which will be described in Chapter X, is not represented in the cases following U.P.A.. The points of difference between the two conditions will be dealt with in Chapter XII.

FOCAL R C.N.

CASE 34. Age 22, para 1, gestation 34 weeks, duration 17 hours. Oedema for 7 weeks previously. Delivered at 11 hours. Became comatose 3 hours p p. and died 6 hours p p. Eclamptic lesions in liver.

CASE 35 Age unknown, para 1, gestation 30 weeks, duration 18 hours. Pre-eclampsia for a few days previously. Eclamptic convulsion 12 hours after U P.A. and delivered one hour later. Died 5 hours p p. Passed 60 cc. urine shortly before delivery and 60 cc. shortly before death. Eclamptic lesions in liver.

CASE 36. Age 32, para 3, gestation 25 weeks, duration 24 hours Oedema for 2 weeks previously. Slight external haemorrhage. Sudden collapse at 24 hours and died undelivered. Complete anuria after U.P.A.

CASE 37 Age 27, para 1, gestation 36 weeks, duration 24 hours. Severe pre-eclampsia previously Became comatose as a result of a large cerebral haemorrhage. Died undelivered

MINOR R.C N.

CASE 38. Age 43, para 15, gestation 36 weeks, duration 14 hours. No external haemorrhage. Delivered at 4 hours. Died in shock 10 hours p p.

CASE 39 Age 30, para 1, gestation 37 weeks, duration 22 hours. Slight external haemorrhage and much vomiting. Became comatose, and died undelivered at 22 hours. Eclamptic lesions in liver.

PATCHY R.C.N.

CASE 40 Age 41, para 9, gestation 34 weeks, duration 18 hours. Oedema for one month previously. Delivered at 13 hours. Erythroblastosis foetalis. Became shocked, and died 5 hours p.p.

CASE 41. Age unknown, para 1, gestation 35 weeks, duration 27 hours. Some external haemorrhage. Delivered at 24 hours. Shock after delivery. Died 3 hours p p. Eclamptic lesions in liver.

GROSS R.C.N.

CASE 42. Age 36, para 9, gestation 36 weeks, duration 8 hours. Slight external haemorrhage. Sudden death undelivered at 8 hours. Eclamptic lesions in liver.

CASE 43. Age 35, para 9, gestation 36 weeks, duration 12 hours. Slight external haemorrhage. Died during labour at 12 hours. Eclamptic lesions in liver. Heart 370 gm.

CASE 44. Age 32, para 4, gestation 39 weeks, duration 14 hours. Some oedema previously Profuse external haemorrhage. Delivered at 11 hours. Much p.p h Died 3 hours p p Eclamptic lesions in liver.

LITERATURE ON EARLY R.C N

Kellar and Arnott (1933, Case 2) record a 3 para aged 30 who developed U P.A. at 31 weeks. She died of eclampsia and cerebral haemorrhage 15 hours after the onset of the U P A The kidney macroscopically showed much congestion of the cortex. The secreting tubules showed advanced cloudy swelling and in some areas had lost their nuclei or were disintegrating; (this description suggests a colloid degeneration with patches of proximal convoluted tubule necrosis) The glomeruli showed marked congestion and haemorrhage and there was much intertubular haemorrhage; (this description corresponds to a stasis-congestion, their Fig 6 is wrongly captioned and is really their Case 2) The case can be accepted as an example of early R C.N., though probably not one which would have been of gross extent.

Ivens (1928, Case 5) gives a report of an 8 para who died 16 hours after the onset of U P.A . The kidney showed hyaline thrombi associated with sharply defined areas of coagulation necrosis The pathological account is inadequate to permit reliable conclusions; this may have been a case of minor R C.N in an early stage, or merely an example of proximal convoluted tubule necrosis with benign glomerular thrombosis

Davidson and Turner (1930, Case 3) record the appearances of the kidney of a 4 para aged 24, who had U P.A at 29 weeks and died 18 hours afterwards. The outer three-quarters of the cortex was very congested. The tubules had swollen granular cytoplasm and much loss of nuclei, more marked in the deeper half of the cortex. The glomeruli showed very marked congestion, and in certain areas there was thrombosis of afferent vessels The case can certainly be accepted as an early stage of R C.N From their Fig. 2, it seems that there was an unusually early development of thin mural thrombosis.

Two further cases in the literature may possibly be early examples of R.C N , but the details are inadequate for reliable diagnosis Seitz (1903, Case 1) records a 5 para aged 28 who had eclampsia and accidental haemorrhage at 31 weeks and died 12 hours later. At autopsy there was an "acute haemorrhagic parenchymatous nephritis". Frankl and Hiess (1921, Case 2) record a primipara who had eclampsia and accidental haemorrhage The time of death is not stated At autopsy there were many little haemorrhages in the renal cortex; this description suggests a focal R C N.

CHAPTER VI

THE PARENCHYMA IN DEVELOPED RENAL CORTICAL NECROSIS

Beginning at about 36 hours, and quite obvious at 48 hours, the area of necrosis becomes differentiated from the surrounding tissue, and various zones can be identified at its margin. The complete picture is seen only if the total area of necrosis is more than about 1.5 mm. in diameter; smaller areas will consist almost entirely of marginal zones

When a large mass of cortex is deprived of its blood supply, the primary lesion is death of all the tissues there. At the outer margin of the resulting totally necrosed mass, there is a broad band of tissue where, as a consequence of collateral capillary circulation, the ischaemia is only partial. This band may be subdivided into an outer *live margin zone* and an inner *zone of partial survival* In the live margin zone there is necrosis of only the most sensitive structures; in the zone of partial survival most of the parenchyma is dead but certain resistant structures have survived.

As a secondary phenomenon, there is an invasion of polymorphs into the dead mass of tissue at the centre. Because of the particular biochemical conditions there, these polymorphs form a band which lies about 200 microns internal to the edge of the totally dead tissue. The dead tissue is thus divided by this *polymorph zone* into a *peripheral dead zone*, external to the polymorph zone, and a *centre dead area*, internal to it. The parenchymal changes in these latter two zones and the centre dead area are essentially similar.

In this way the centre dead area is surrounded by four concentric zones. Each of these zones merges gradually into the next one, and the live margin zone similarly merges into the surviving tissue around. Though in the following descriptions the appearance of each zone is described separately, it must be made clear that there is no line of absolute demarcation between them except at the inner margin of the polymorph zone, which is usually sharp.

The description of the processes of repair will be deferred to Chapter VIII.

LIVE MARGIN ZONE (Fig. 25)

In this zone there is necrosis of all the proximal convoluted tubules. The necrosis-changes progress at the same rate as those described under the heading of proximal convoluted tubule necrosis. A few glomeruli may have benign thrombosis of capillaries or stalk afferent vessels, or even dilatation and congestion of some of their loops. From the time when this zone first becomes



Fig 25 Junction of live margin zone on right and remaining cortex on left, in early gross R C N 36 hours after U P A



Fig 26 Zone of partial survival in early gross R C N The distal convoluted tubules remain alive 36 hours after U P A

recognisable, at 36 hours, there is never any evidence of further necrosis in it, neither a necrosis of hitherto surviving tubules nor an extension of the area of R.C.N. As will be discussed later, this last statement is in disagreement with the views expressed by some previous authors. It is however based on a meticulous examination of every kidney with R.C.N. in the present series.

ZONE OF PARTIAL SURVIVAL (Fig. 26)

This zone is characterised by the necrosis of some structures of the parenchyma, and by the development of congestion of glomeruli and intertubular capillaries. The zone varies from about 100 to 300 microns in depth.

The necrosis-changes in the proximal convoluted tubules are in general rather similar to the necrosis-changes in [illegible] but the nuclei disappear more slowly an[illegible] 36 hours. The distal convoluted tubules and the collecting tubules remain healthy, apart from sometimes a slight loosening of their epithelium from the basement membrane.

The glomeruli show a variable congestion, sometimes of only part of the tuft and sometimes of every capillary loop. The endothelial nuclei in the congested loops are flattened to thin crescents at 36 hours, and have disappeared within 2 or 3 days. The epithelial cells over the tuft sometimes disappear at about the same time, but a few of these cells are usually left intact. The red corpuscles in the congested loops have lost their haemoglobin by about 36 hours, and they have degenerated within about 3 days to a little finely granular debris.

Deeper in the area, other glomeruli, which have not been significantly congested, undergo a particular type of necrosis which usually involves the whole tuft but may affect only some of the lobules. Most of the nuclei become pyknotic and disappear, though some epithelial nuclei and occasional endothelial nuclei survive. There is usually a fine dust of lipoid throughout the tuft. The stalk afferent vessels are frequently dilated and sometimes thrombosed. The necrosed glomeruli, or necrosed lobules of glomeruli, lose their capillary outlines at about 3 or 4 days and shrink down, soon after, to a rounded mass of loosely granular debris on whose surface occasional epithelial cells remain.

A variant of this glomerular lesion is sometimes seen in the outer part of the zone of partial survival. That half of the tuft which faces the necrosed area becomes congested and undergoes complete necrosis. The other half of the glomerulus remains quite normal and is sharply demarcated from the necrosed part of the tuft (Fig. 27). There is no recognisable thrombosis in the stalk afferent vessel or capillary loops, to account for this very sharp division.

The intertubular capillaries are congested by fresh blood, in which the red corpuscles stain normally and the leucocytes are cytologically quite healthy. It seems probable that this blood is still slowly circulating from and to the capillaries in the neighbouring live tissue. Most of the endothelial nuclei of



FIG. 27 Necrosis of half of glomerular tuft in zone of partial survival in patchy R C N 2½ days after U P A



FIG. 28 Congested glomeruli in zone of partial survival in patchy R C N 2½ days after U P A (Magnification × 4)

these intertubular capillaries in the zone remain fairly healthy, though a few of them become flattened and darkly staining. In certain places there is an extreme congestion of the intertubular capillaries. This is related to a small group of congested glomeruli whose efferent arterioles are packed with red corpuscles and occasionally contain some fibrin; in the vicinity there is usually a grossly congested vein.

There is not infrequently some haemorrhage into the lumen of the necrosed proximal convoluted tubules in the area. This blood may be seen lying either inside or outside the stripped sleeve of necrosed epithelium. Sometimes it pushes the necrosed epithelium down to plug the lumen below, and then the upper loops of the tubules appear merely as lumina distended with red corpuscles

In the early stages, the congestion is very diffuse and irregular. From 48 hours onwards it becomes more clearly confined to this zone, and is usually more marked in the glomeruli than in the intertubular capillaries (Fig. 28). The congestion remains recognisable in the subcapsular area until about 8 days, and in patches in the deep cortex for over 15 days. It is always very prominent in the bands of partially surviving tissue which radiate in places through the cortex.

At 36 to 48 hours there is usually a rather diffuse infiltration of polymorphs throughout this zone, but subsequently these cells are less common and very few are seen after about 5 days.

The arteries traversing this zone participate in the same changes as those in the peripheral dead zone; these lesions will be described in the next Chapter.

PERIPHERAL DEAD ZONE (Fig. 29)

In this zone there is necrosis of all the parenchyma. The zone is about 100 to 200 microns in depth.

All the tubules die, though their nuclei may take considerably over 36 hours to disappear The necrosis of the distal convoluted tubules and the collecting tubules differentiates this zone from the zone of partial survival. The glomeruli lose all traces of their epithelial and endothelial nuclei within about 4 days, and the nuclei of the intertubular capillaries disappear in the same period Some of the dead glomeruli retain their capillary pattern, but in the more peripheral glomeruli the loops may be obscured by a general disintegration of the structure of the tuft.

There is a variable amount of congestion at 2 to 3 days, involving some of the intertubular capillaries and a few of the glomeruli These red corpuscles rapidly lose their haemoglobin and have disintegrated at 3 to 4 days. Some polymorph infiltration is present at 36 to 48 hours, but much of this disappears *within the next 2 or 3 days.*

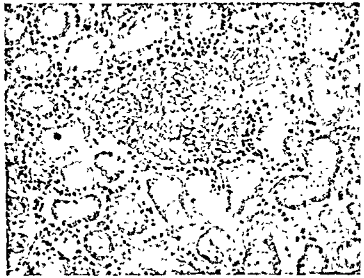


FIG 29 Peripheral dead zone in gross R C N, showing necrosis of all structures but retention of nuclear shadows 5½ days after U P A.



FIG 30 Junction of polymorph zone on left with centre dead area on right 36 hours after U P A

POLYMORPH ZONE (Fig. 30)

This zone forms the outer edge of the centre dead area, and differs from this area only in that its intertubular capillaries are packed with polymorphs. The renal parenchyma and interstitial tissue is dead, but the rate of disappearance of nuclei is slow: about the same rate as in the centre dead area to be described in the next section

The zone is first recognisable at about 36 to 48 hours, when the polymorphs that have been infiltrating diffusely through the outer zones penetrate further into the dead tissue. Here they become concentrated as a band, whose internal edge is quite sharp but whose outer edge merges into the diffuse polymorph infiltration further out At 72 hours this band forms a well-defined zone about 100 to 250 microns in depth. The polymorphs here are mainly concentrated in the intertubular capillaries, though they may extend a little into the necrosed parenchyma.

For the first two or three days these cells appear relatively healthy. At 5 days the leucocytes at the inner margin of the polymorph zone disintegrate to a dirty basophil debris. Within the next day or two the whole band disappears, leaving only this thin line of debris, which remains recognisable for another day or so. These changes are paralleled by the alteration of the lipoid staining reactions of the cells. During the first 48 hours the polymorph granules stain in the normal way with Sudan Black but not with Sudan Red (Sheehan, 1939; Sheehan and Storey, 1947) During the next two days the granules change in character so that they take both stains equally well and, when the leucocytes disintegrate, they leave small globules with the ordinary appearance and staining reactions of fat.

This general course is slightly modified according to the site in the renal cortex. The subcapsular band of polymorphs is usually not more than 200 microns in depth, and has always disappeared completely at 8 days. The band in the deeper cortex is usually rather wider and may vary up to 300 or 400 microns. In addition, in any area of gross R.C.N. there are, at irregular intervals, broad columns of polymorphs which radiate out from the juxta-medullary edge of the necrosed area towards the surface of the kidney. These appear to be minor examples of the radial bands of partially surviving tissue seen elsewhere in the cortex. In these radiating bands, and in the deeper part of the cortex, the polymorph zone usually remains longer than in the sub-capsular region, and is present, though patchy, in some cases as late as 9 days.

CENTRE DEAD AREA

When the total area of necrosis is large, all the marginal zones are present to their full depth, and enclose an area of dead tissue at the centre. The earliest stages of the death of this area have been described previously, but it

is only from about 36 to 48 hours that the area becomes clearly delimited by the inner margin of the polymorph zone.

The main features are the total death of all structures and the slow rate of necrosis-changes in them. Red corpuscles and leucocytes are absent from the area

Proximal convoluted tubules At 36 hours these show the two appearances described in Chapter V dealing with the early stages of R.C.N.: (a) Some of the tubules have small and strongly staining nuclei, and the epithelial cytoplasm, though rather faded, retains its normal structure. (b) Other tubules retain the characteristic appearance of the arrested tubular necrosis. They have the sleeve-separation of dead epithelium, with radial fracturing of the sleeves Their nuclei are shrunken and pyknotic but still stain excellently

The nuclei begin to fade slowly at about 72 hours. At 5 or 6 days some of them are no longer recognisable, but the majority still stain fairly well (Fig. 31) They disappear one by one until, at about 10 days, none remain The cytoplasm is so excellently preserved that at 10 days the structure is the same as it was at 36 hours, there is never any disintegration into amorphous debris (Fig. 32) Some weakly basophil fluid may be present in the lumen of the tubules between the 3rd and 7th days.

It will be clear that these changes in totally ischaemic tissue in the living body are quite different from those of post-mortem autolysis in the dead body In addition, it should be noted that at no stage is there any recognisable swelling of the dead parenchyma (cells) by imbibition of fluid, such as is commonly postulated as an essential part of "coagulative necrosis" Calcification in dead tubules has *not been seen in the present series, but was recorded by* Iungano (1927) and Åkerrén (1947).

Nearly all the spiral segments have their lumen loosely filled by desquamated epithelial cells The nuclei of these cells have usually disappeared completely by about 5 or 6 days, but the cellular outlines remain quite clear at 10 days

Distal convoluted tubules A thin and weakly basophil gelatinous fluid appears at about 36 hours between the desquamated epithelial cells of the distal convoluted tubules, particularly near the edge of the centre dead area. At about this time, the nuclei of these cells, though still well staining, become distorted to a thorn-apple appearance At 5 days the nuclei begin to fade, but the intercellular basophil fluid in the lumen is considerably increased in amount Most of the nuclei have disappeared at about 7 or 8 days, but the basophil fluid is still recognisable up to about 10 days

Previous tubular lesions. It is important to record that in the centre dead area there are no remains of albuminuria casts, of colloid casts in the distal convoluted tubules, nor of hyaline droplets in the proximal convoluted tubules. If these lesions had occured in the centre dead area during the early stages of its development, they ought certainly to be still recognisable, in view of the

POLYMORPH ZONE (Fig. 30)

This zone forms the outer edge of the centre dead area, and differs from this area only in that its intertubular capillaries are packed with polymorphs. The renal parenchyma and interstitial tissue is dead, but the rate of disappearance of nuclei is slow: about the same rate as in the centre dead area to be described in the next section.

The zone is first recognisable at about 36 to 48 hours, when the polymorphs that have been infiltrating diffusely through the outer zones penetrate further into the dead tissue Here they become concentrated as a band, whose internal edge is quite sharp but whose outer edge merges into the diffuse polymorph infiltration further out. At 72 hours this band forms a well-defined zone about 100 to 250 microns in depth. The polymorphs here are mainly concentrated in the intertubular capillaries, though they may extend a little into the necrosed parenchyma.

For the first two or three days these cells appear relatively healthy. At 5 days the leucocytes at the inner margin of the polymorph zone disintegrate to a dirty basophil debris. Within the next day or two the whole band disappears, leaving only this thin line of debris, which remains recognisable for another day or so. These changes are paralleled by the alteration of the lipoid staining reactions of the cells During the first 48 hours the polymorph granules stain in the normal way with Sudan Black but not with Sudan Red (Sheehan, 1939, Sheehan and Storey, 1947). During the next two days the granules change in character so that they take both stains equally well and, when the leucocytes disintegrate, they leave small globules with the ordinary appearance and staining reactions of fat.

This general course is slightly modified according to the site in the renal cortex. The subcapsular band of polymorphs is usually not more than 200 microns in depth, and has always disappeared completely at 8 days. The band in the deeper cortex is usually rather wider and may vary up to 300 or 400 microns In addition, in any area of gross R.C.N. there are, at irregular intervals, broad columns of polymorphs which radiate out from the juxta-medullary edge of the necrosed area towards the surface of the kidney. These appear to be minor examples of the radial bands of partially surviving tissue seen elsewhere in the cortex In these radiating bands, and in the deeper part of the cortex, the polymorph zone usually remains longer than in the sub-capsular region, and is present, though patchy, in some cases as late as 9 days.

CENTRE DEAD AREA

When the total area of necrosis is large, all the marginal zones are present to their full depth, and enclose an area of dead tissue at the centre. The earliest stages of the death of this area have been described previously, but it

fact that the arrested early stages of proximal convoluted tubule necrosis can be identified so easily. Nevertheless it is certainly possible that some of the tubules may have passed through a phase of colloid degeneration which can no longer be identified in the dead tubules. This is suggested by the biopsy case (Case 64) which at 36 hours showed, in a few areas, tubules which had clearly suffered a colloid necrosis. In the same kidney at autopsy at 8½ days, it could not be recognised that any tubules in the centre dead area had undergone this particular type of necrosis, but a clue to such a previous course was provided by the presence of colloid casts in the intermediate zone.

Interstitial tissue There is pyknosis and early fading of endothelial nuclei from 36 hours onwards, and most of these nuclei have disappeared at 6 to 8 days Any red corpuscles in the capillaries have lost their haemoglobin by 36 hours, and have disappeared completely at 48 hours. With formalin fixation, formalin pigment may be present in considerable amount between the tubules at about that time

Throughout the area, the intertubular spaces are considerably widened by a weakly basophil oedema fluid, in which the original site of the capillaries can not easily be identified This begins at about 36 hours, increases to about 5 or 6 days, and is still obvious at about 10 days. It is presumably a result of seepage of fluid from the neighbouring live tissue; a seepage which probably accounts for the basophil gelatinous fluid in the distal convoluted tubules This intertubular oedema in the cortex explains much of the great increase in weight of the kidney in R C N ; the possible occurrence of a similar oedema in the medulla can not be assessed very satisfactorily

Glomeruli Most of the glomeruli show no evidence of previous congestion Their capillary loops are not dilated. At 36 hours their endothelial nuclei are pyknotic and a little flattened, but are not distorted into a crescentic shape. The epithelial nuclei develop a smudgy chromatin but do not become pyknotic At 72 hours many of the nuclei are fading, and a peculiar finely granular and weakly basophil material is appearing in the capillary loops This material increases to about 5 or 6 days and then slowly disappears. Most of the nuclei have lysed at 5 or 6 days, but the shrunken remains of occasional nuclei may persist even longer than 10 days

In a small number of the glomeruli there appears to have been congestion before the complete necrosis developed. At 36 hours these can be recognised easily because the loops are distended by red corpuscles, whose haemoglobin has disappeared but whose outlines are maintained. The endothelial nuclei of these loops show the usual compression to a thin crescentic shape and are deeply pyknotic. At 48 hours the remains of these red corpuscles have disappeared, leaving a scarcely perceptible trace of fine debris in the lumen The capillary loops may remain dilated for another day or two The endothelial nuclei retain their flat crescentic shape and may still be stained as late as 5



Fig 31 Centre dead area in gross R C N, showing retention of nuclei in dead tubules. 6½ days after U P A (Compare with Fig 21).

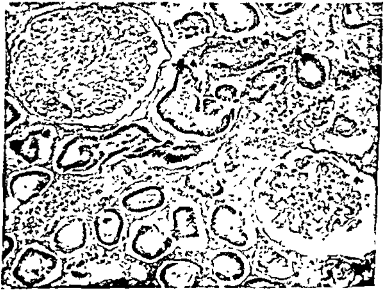


Fig. 32 Centre dead area in gross R C N, showing preservation of fractured sleeves of the proximal convoluted tubule necrosis which had occurred during the first few hours. 8½ days after U P A.

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to 7 days When these nuclei have faded, there is no remaining clue to the previous state of these glomeruli, apart from occasional herniation of the tuft into the mouth of the proximal convoluted tubule.

Some glomeruli were described in the account of the earlier stages in Chapter V as showing thrombi in loops or fat deposition in the endothelium. These appearances remain unaltered in the centre dead area for, at any rate, 15 days. In many glomeruli, particularly those which have plaster thrombus in the stalk afferent vessel (an appearance to be described in the next Chapter), there is a heavy powdering of fat in the dilated wall of that vessel and in the endothelial cells of most of the capillary loops. This fat is present at 36 hours and remains unchanged for at least 9 days.

Pre-existent cortical lesions A point of considerable interest is that in the necrosed area there are never any old lesions such as hyalinised glomeruli or areas of cortical scarring This may be because such scars are usually subcapsular, and also because their vascular supply is very different from the normal. Furthermore, there are never any necrotic ghosts of glomerular crescents, arterial changes, or other lesions suggestive of a pre-existent nephritis. Similarly there are never any necrotic ghosts of recently repaired parenchyma, such as would be seen if the area of necrosis became more extensive several days after its original occurrence

REMAINDER OF THE KIDNEY

There are always some areas of cortex remaining unaffected by the R.C.N.. These areas of *remaining cortex* show a variety of lesser lesions, some of which are the same as those seen in the live margin zone. In fact the outer edge of the live margin zone can sometimes only be delineated from the remaining cortex by its situation around an area of cortical necrosis.

Most of the glomeruli in the remaining cortex are healthy but, in the tufts where benign glomerular thrombosis had occurred in the early stages, these thrombi are still recognisable several days later.

A high proportion of the nephrons show ordinary proximal convoluted tubule necrosis. As most of the patients have survived for 5 to 12 days, these tubules are in process of repair, usually with much increase of interstitial tissue. In cases of focal R.C.N. there is so much remaining cortex that the proximal convoluted tubule necrosis is a very prominent feature.

Any colloid degeneration which had occurred earlier in proximal convoluted tubules has at this stage either proceeded to full necrosis and repair, or has resolved completely.

The number of relatively healthy proximal convoluted tubules is always small: about one-third of the nephrons in the remaining cortex in the cases of focal R.C.N., and only a very small fraction of them in the cases of gross R.C.N.. However, even in the most extensive cases, a few surviving proximal

convoluted tubules can always be found; these lie mainly in the juxtamedullary zone, but they are sometimes present under the capsule or in the radiating bands through the cortex. Their epithelium may show hyaline droplet formation and, after a couple of weeks, they may become dilated. For a short period at about 7 to 9 days, a basophil fluid sometimes appears in the lumen of the first few loops of these tubules. In half of these cases the fluid is also seen in the capsular space of the related glomeruli. Its aetiology and significance are not clear.

The distal convoluted tubules in this remaining cortex are unchanged until about 12 days, after which time their epithelial cells may proliferate so that the tubules have twice as many nuclei as normal. The subsequent course of this proliferated epithelium cannot be followed in the present material.

As has been mentioned previously, about one-third of the cases of R.C.N. show a considerable formation of colloid casts in the tubules of the intermediate zone. These casts remain quite unaltered in cases as late as 10 days. In the literature, there are frequent reports of hyaline casts in the medulla or in the unaffected parts of the cortex in cases of R.C.N.. It is possible that some of these were albuminuria casts in collecting tubules, but many were probably colloid casts in the intermediate zone or in the loops of Henle in the medulla. The descriptions are almost always inadequate to decide their true nature: Bradford and Lawrence (1898), Zaaijer (1903), Lloyd (1906), Griffith and Herringham (1906), Schuppel (1914), Geipel (1914), Bowes (1934), Bruno (1941), Adam (1945), Lowrie and O'Connell (1950).

[illegible] ain large numbers of [illegible] R.C.N. is of only [illegible] usually smaller. The [illegible] intermediate zone in cases where these collecting tubule casts are present.

OTHER CHANGES

In cases at about 2 to 4 days there is usually much perirenal oedema, which may be lightly haemorrhagic. At about a week, the perirenal fatty tissue becomes extremely tough and adherent to the outer surface of the capsule, though the capsule itself can be stripped from the kidney without much difficulty. Microscopically, the perirenal fat and the capsule usually show large numbers of dilated and congested vessels, and sometimes contain numerous polymorphs.

The appearances may be further complicated by an incidental pyelonephritis, which sometimes results from the repeated catheterization of these oliguric patients. Though this can be of considerable clinical significance, it is irrelevant to the pathology of R.C.N.

CHAPTER VII

THE ARTERIES IN DEVELOPED RENAL CORTICAL NECROSIS

The early lesions in the arteries and glomeruli have been described in a previous section:—thrombosis or stasis in glomeruli, necrosis of the walls of arteries and dilatation of these vessels, and the formation of solid thrombi in occasional small arteries in cases of minor R.C.N.. The further developments from 36 hours onwards consist of thrombosis of other arteries and certain related lesions in the arterial walls, including a process which is described here as basophil *intimitis.*

GENERAL CONSIDERATIONS OF THE THROMBOSIS

The structure of the arterial thrombi has been a matter of some debate. Fibrin stains are notoriously fickle, and depend to some extent on fixation; this probably accounts for many of the discordant reports in the literature. In the present series, most thrombi stain well by Weigert's method for fibrin but a few give negative results. Thin fibrillar thrombi usually stain excellently by this method, but the central parts of some solid thrombi, such as in the columns of trellis thrombus, may stain only a pale translucent green.

The more solid thrombi have either a hyaline or a finely granular appearance similar to that seen in small vegetations on heart valves. This type is usually referred to as a platelet thrombus. Platelets may well be one of the main constituents, particularly at the proximal end of solid occlusive thrombi, but it is impossible to identify the platelets at this stage. The thrombi commonly show a fine powdering with fat; this may possibly derive from the disintegration of leucocytes, but its exact origin has not been determined

A view that has been put forward by Navasquez (1935) is that the arterial thrombi are formed by the conglutination of red corpuscles into a solid mass, which remains unchanged for at any rate several days. This hypothesis cannot be accepted. It has been explained previously that stagnant red corpuscles in an area of ischaemic parenchyma disintegrate within about a day after they have become stationary; only a negligible amount of stroma debris then remains from a mass of red corpuscles which originally filled the lumen. This objection does not apply to the continued survival of a mass of packed red corpuscles in the presence of actively circulating blood, nor to the gradual formation of a type of thrombus from the debris of a very great series of conglutination-disintegration sequences. Such explanations could however

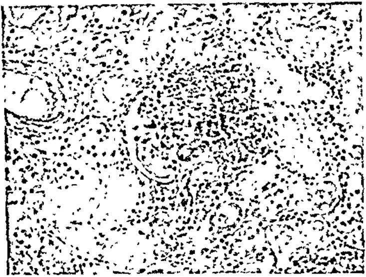


FIG 33 Focal R C N, showing necrosis and thrombosis of afferent arteriole and stalk afferent vessel, and thrombosis and stasis in the capillary loops of the dead glomerulus 3 days after U P A

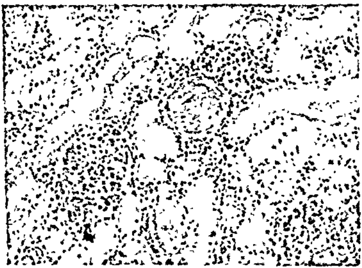


FIG 34 Minor R C.N showing dilatation and solid thrombosis of the necrosed arteries. 3 days after U P.A

only apply to the proximal surface of solid occlusive thrombus in large arteries and, in fact, no conglutination of red corpuscles is ever seen on this surface.

DETAILS OF ARTERIAL LESIONS

From 36 hours onwards, the affected arteries show a uniform dilatation and have a well developed necrosis of their walls, progressing at about the same rate as the necrosis of the interstitial tissue around them. The layers of the wall become blurred within 2 or 3 days, though the pyknotic nuclei of the media can still be recognised for several days in the centre dead area. The fine fat, which had previously appeared in the media, may also remain for several days Any red corpuscles in the wall become dehaemoglobinised, and disappear within about 2 days.

The development of the various types of thrombi may best be considered in relation to the size of the artery affected. This order corresponds roughly to the time of occurrence of the thrombosis and to the extent of the areas of R.C.N.

SOLID THROMBUS IN FOCAL AND MINOR R.C.N. (Figs. 33 and 34)

The thrombosis of stalk afferent vessels and afferent arterioles in focal R.C N., and of small arteries in minor R.C.N., is first observed at about 14 hours, as has been described in detail in the Chapter on the early stages of R.C.N. These thrombi appear firm and solid, and occlude the dilated lumen. They remain visible for several days longer, and are finally submerged in the organisation process which develops in these small areas of R C.N.

TRELLIS THROMBUS (Fig. 35)

This type of thrombus develops characteristically in cases of patchy R.C.N., but it is seen in some cases of gross R.C.N.. It involves the intralobular arteries at about a quarter to half way from the medulla to the renal capsule, and may obstruct the vessel for a distance of up to 500 microns. It is seen first at about 36 hours, *and is present in all cases after that time.*

The thrombus is built up as columns or septa of densely granular or hyaline structure, forming a trellis across the entire lumen of the dilated artery. There are numerous gaps between the columns, so that the lumen of the vessel is not obliterated. The bases of the columns are firmly adherent to the intima, and in many places there is a thick layer of thrombus along the entire wall. The material of the thrombus is usually well demonstrated by fibrin stains, except in the centre of the columns near its proximal end.

In the early stages, at 36 hours, polymorphs are sometimes attached to the surface of the columns. The spaces between the columns are filled at this time by a coagulum consisting almost entirely of packed red corpuscles; some of these corpuscles stain normally, while others are *dehaemoglobinised.*



FIG. 35. Trellis thrombus in a necrosed intralobular artery in early gross R.C.N. 36 hours after U.P.A.

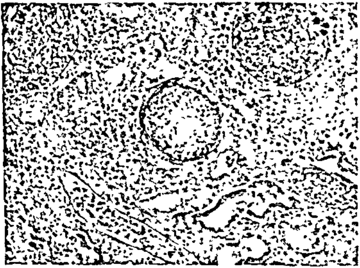


FIG. 36. Late stage of trellis thrombus, showing red corpuscles which have recently entered the artery and are packed in a segment where there happens to be very little thrombus. 9 days after U.P.A.

At 66 hours the polymorphs have disintegrated to a basophil debris which outlines the clefts in the trellis. Most of the red corpuscles in the lumen have now disappeared so that the coagulum is no longer recognisable.

At various times after this, there may be a filling-out again of the spaces of the trellis with red corpuscles, which are sometimes normally staining, sometimes dehaemoglobinised, and sometimes in process of disappearance. These corpuscles may be so closely packed together, and the septa of the trellis so widely separated, that it appears in certain transverse sections as if the artery were entirely occluded by red corpuscles (Fig. 36); in other transverse sections it seems to be entirely occluded by solid thrombus.

THICK MURAL THROMBUS (Fig. 37)

This type of thrombus is seen in arteries of moderate size in the dead area, mainly in the peripheral dead zone and polymorph zone. In most cases it is a distal prolongation from a trellis thrombus. In patchy R.C.N. it continues for a considerable distance along the dead arterial tree, but in gross R.C.N. it is usually much less extensive.

It consists of a layer of dense thrombus, about 15 to 40 microns deep, forming a thick tube which is commonly adherent to the intima but may be separated from it by a small gap. This reduces the lumen of the artery to about one-half to two-thirds of the overall diameter. The thrombus always stains well by Weigert's fibrin method.

Thick mural thrombus occurs first in the present series at 36 hours, and remains unchanged in the dead area for at least two weeks.

THIN MURAL THROMBUS (Fig. 38)

This type of thrombus is characteristically seen in cases of gross R.C.N.; it is confined to the centre dead area, the polymorph zone and the peripheral dead zone. It occurs sometimes in patchy R.C.N., but naturally can not be seen in the cases of less extensive R.C.N. where the lesions do not include a centre dead area.

The condition consists of the application of a thin lamina of loose or fibrillar fibrin thrombus to the endothelial surface throughout the dead arterial tree. The thrombus is about 5 to 10 microns in thickness, so that it encloses a wide lumen. It may be closely applied to the endothelium or may be separated from it by a space. In the arteries it tends to be loosely attached to the wall until it reaches the mouth of an arteriole. Here it is more firmly adherent and is thicker, so that the two surfaces of the thrombus are almost in contact and virtually occlude the entrance to the vessel. It continues as a rather looser thrombus up the arteriole until it reaches the glomerulus (Fig. 39). At the stalk afferent vessel, which is always dilated to a miniature bulbous aneurysm, it forms a thick plaster closely applied to the inner surface of the wall (Fig. 40).

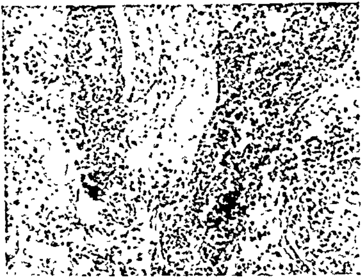


FIG 37 Thick mural thrombus in early gross R C.N 36 hours after U.P.A



FIG 38 Thin mural thrombus in the centre dead area of a gross R C N 8½ days after U P A.



Fig 39 Thin mural thrombus in intralobular artery and afferent *arteriole in the centre dead area of gross R C N 8½ days after U P.A*

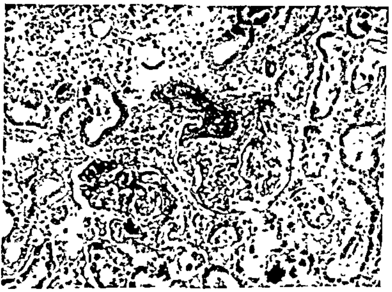


Fig 40 Thin mural thrombus in afferent arteriole, and plaster thrombus in the dilated stalk afferent vessel, *in the centre dead area of* patchy R C N.. 2½ days after U P.A

Sometimes there is a tubular process of the mural thrombus extending into one or two capillary loops of the tuft; these may be difficult to distinguish from benign glomerular thrombi In the stalk afferent vessel, the lumen inside the plaster thrombus is nearly always filled with a looser skein of fibrin.

In most cases the thin mural thrombus involves the whole arterial tree including the stalk afferent vessels; sometimes it is seen only in the arteries but not in the glomeruli; occasionally it is scarcely formed at all, even in the arteries.

It is not seen before 36 hours, but is present in practically every case of gross R.C N from this time onwards, and remains easily recognisable for at least 10 days.

BASOPHIL INTIMITIS

This name describes the development in the arteries, inside an extensive area of R C N., of a sub-intimal polymorph infiltration which subsequently degenerates into a dirty basophil spongework. It is confined entirely to the dead dilated arteries in the centre dead area of the R C.N.. This lesion has previously been recorded by Herzog (1913, Case 3) and Hugin (1946, Case 1).

Basophil intimitis does not begin until there is an early polymorph zone around the centre dead area The initial condition, which is seen at 36 hours, is a raising of the endothelium by an infiltration of inflammatory cells These are mainly polymorphs but, in addition, there are a number of mononuclear cells of undetermined type, possibly histiocytic (Fig 41) At this stage the endothelium over the "blister" is still recognisable and continuous The media is necrosed, but usually contains no polymorphs or red corpuscles.

By 48 hours there is a peculiar vacuolation and swelling of the cytoplasm of these [illegible]
nuclei [illegible]
and be [illegible]
The nuclei of all the cells become compressed to very thin crescents around the periphery of the cell, and their chromatin seems to diffuse out into the cytoplasm. The resultant appearance is a sponge of coarse smudgy basophil debris, containing the flattened or crescentic remnants of nuclei and a variable amount of fat in fine droplets. This forms a layer which may be even twice as thick as the media, and lies completely on the luminal side of the internal elastic lamina (Fig 42). It has an ill-defined inner surface if no thrombosis occurs over it The lumen of the vessel remains widely patent owing to the dilatation of the wall

After the basophil sponge has developed, a layer of thin mural thrombus is nearly always deposited on its surface, and firmly attached to it by short fibrin rootlets, which pass down between the remains of the cells and may penetrate through into the necrosed media (Fig. 43).

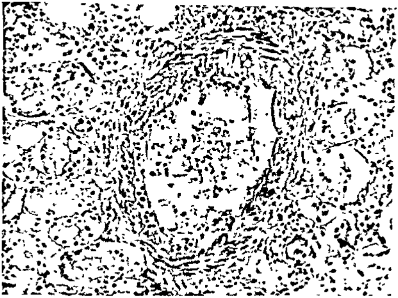


Fig 41. Very early stage of basophil intimitis in centre dead area of gross R C N 2 days after U P A



Fig 42. More advanced stage of basophil intimitis. 2½ days after U.P.A



FIG. 43. Deposition of thin mural thrombus over the inner surface of basophil intimitis 6½ days after U.P.A.

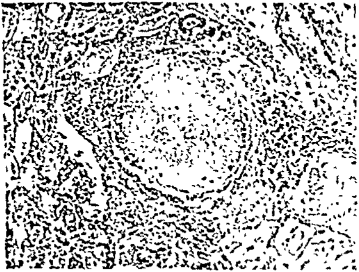


FIG. 44. Occlusive thrombus in the lower part of an intralobular artery in gross R.C.N., 10 days after U.P.A.

The condition affects the intralobular arteries and is occasionally seen to a much slighter degree in a few afferent arterioles, but it only rarely reaches to the stalk afferent vessels. It spreads along the branches of certain arterial trees, leaving neighbouring arterial trees unaffected. Its distribution along an artery tends to be patchy, sometimes involving the whole circumference of a long segment, and sometimes scattered as poorly developed foci in small areas along the wall

The basophil intimitis has the same duration as the polymorph zone. It begins at about 36 hours; it can still be seen in a degenerate form at 5 to 6 days and, in one case, could be recognised as late as 9 days. Sometimes, in the very late cases, what seems to be a simple thin mural thrombus may be observed to have the fibrin rootlet pattern; this is presumably the site from which an original basophil intimitis has disappeared.

OCCLUSIVE THROMBUS IN LARGE ARTERIES (Fig. 44)

When extensive R.C N has been present for a few days, the large intralobular arteries become occluded by a solid plug of hyaline or granular thrombus at the level where they pass from live into dead tissue. This fills the whole lumen of the artery and is attached to the intima over most of its circumference; it extends about 100 to 200 microns in length. In cases where there has been a trellis thrombus in the artery, the occlusive thrombus is built up directly on the proximal end of the trellis In other cases it is formed *de novo*, and the distal parts of the artery show only thin mural thrombus.

Occlusive thrombosis has not been observed in cases of gross R.C.N at 2 and 3½ days It is present in all cases of this severity from 5 days onwards, and presumably develops in the interval between 3½ and 5 days

SPECIAL LITERATURE

From this analysis of the arterial changes, an explanation can be offered for the four charts of the distribution of arterial thrombosis and necrosis given by Navasquez (1935). Most of his cases appear to have been gross R C.N., though his Case 2 was an early patchy R.C.N., and his Case 9 may have been a severe patchy R.C.N. The arteries that he classified as necrosed and dilated can be accepted as such without question. On the other hand he has a somewhat rigid concept of thrombosis, and includes only what is called here trellis thrombus and occlusive thrombus in large arteries. He did not find fibrin in any of the thrombi, and appears to describe mural thrombosis as "hyaline necrosis". His charts, if interpreted in this way, can be brought into general agreement with the findings in the present series.

OTHER CONTENTS OF DEAD ARTERIES

The stagnant blood in the lumen beyond an occlusive thrombus probably

always undergoes simple coagulation. This occurs in the interstices of a trellis thrombus or in a vessel with either variety of mural thrombus lining its wall. The clot consists of very numerous red corpuscles and a few leucocytes, entangled in a fine meshwork of fibrin. As the area is ischaemic, the corpuscles become dehaemoglobinised at about 10 or 12 hours after the coagulation, and disintegrate within another 10 or 12 hours At this stage, all that is left of the original massive clot is a little wispy tangle of fibrinous debris in the centre of the lumen This scrap of debris can easily be overlooked, and thus an artery may be considered empty which was in fact filled with clot 24 hours earlier. Most of the simple coagulation in arteries in R.C.N seems to occur at about 18 to 36 hours, the clots have practically disappeared at 40 to 60 hours.

From 5 days onwards, occasional red corpuscles or leucocytes may be seen free in the lumen of the arteries distal to the main thrombus. These cells may be quite normal in staining and general appearance, or there may be dehaemoglobinisation of the corpuscles and obvious degeneration of the leucocytes. The occurrence of fresh red corpuscles in the distal parts of the dead arteries and in neighbouring capillaries may lead to some histological confusion with the true congestion of the zone of partial survival, the condition is easily recognised by reference to the state of the surrounding parenchyma It may be accepted that this blood in the necrosed area has oozed past the occlusive thrombus, and that the red corpuscles, being still recognisable, must certainly have entered the vessel during the day before the death of the patient This ooze of blood probably occurs at intervals in most cases, but it is too trivial to have any effect on the parenchyma, and leads merely to trapping of the red corpuscles in the dead artery at this stage. The true re-establishment of a bloodflow at about 2 weeks will be described in the next *Chapter*

PANARTERITIS

At the point where the thrombosed arteries pass through the polymorph zone, there is not infrequently some leucocytic invasion from the surrounding tissue into the media This is usually quite slight, but in three cases in the present series, at 5 to 6½ days, this invasion was very prominent around some of the large intralobular arteries Polymorphs accumulated heavily in the adventitia, penetrated the media at various places, and finally spread along clefts in the occlusive thrombus, where they degenerated to the characteristic basophil debris In places, some blood had escaped through the disintegrated media and formed a zone of haemorrhage between the media and the zone of heavy leucocytic infiltration of the adventitia It is of interest that there was no severe haemorrhage from these arteries affected by panarteritis. This supports the idea that this late flow of blood into the arteries is not of great volume and is at low pressure

VEINS

In rather over half of the cases of R C.N. before 36 hours, and in many cases of the lesser lesions at any time, there is in histological sections a prominence of some of the cortical veins, particularly those in the deep cortex. This prominence appears to be due to failure of the particular vein to collapse after the death of the patient. The lumen may be empty or may contain some clot. Precisely the same appearances are seen commonly in normal kidneys, and therefore can not be regarded as of pathological significance.

In R.C N. of over 36 hours duration, the veins are collapsed and difficult to find in three-quarters of the cases. This is particularly so in the centre dead area. In each of two cases of severe R C.N. of about 7 days' duration, a single cortical vein in the zone of partial survival was thrombosed and showed early organisation The fact that these were the only venous lesions observed in the whole series suggests that they were secondary and incidental

The differentiation of a dead and dilated artery from a vein can be difficult It seems that, in a few of the older descriptions of R.C.N., the thrombosis of arteries was in fact described as thrombosis of veins, but there can be no doubt that some of the descriptions were reliable and that venous thrombosis was actually present If septic thrombosis of the left ovarian vein occurs, it sometimes gives a retrograde thrombosis in the renal vein. Among the following reports of venous thrombosis in cases of R.C.N., there are examples of true thrombosis of veins and also of misinterpretation of dilated arteries:—Poten(1906), Jardine and Teacher (1911, Cases 1 and 2), Torrens (1911), Rolleston (1913), Jardine and Kennedy (1913, Case 1), Westman (1928, Case 1), Davidson and Turner (1930, Case 4), Lieu (1938), Weaver and Haam (1939), Brown and Crane (1943). Reviews of other cases, where thrombosis of renal veins gave a combination of medullary and cortical necrosis of the kidney, have been written by Herzog (1913), Swaab (1939), and Larson and Bennett (1939).

CHAPTER VIII

HEALING STAGES OF RENAL CORTICAL NECROSIS

REPAIR PROCESSES IN THE NECROSED AREA

LIVE MARGIN ZONE (Fig. 45)

The initial stages of repair are seen at about 4 days in the live margin zone. Regeneration occurs in the proximal convoluted tubules there, exactly as described in Chapter IV in the section dealing with simple necrosis of those tubules. Within another day or two, the tubules in this zone are well regenerated; their lumina are sometimes filled by debris, and are sometimes empty apart from desquamated new epithelial cells which often contain fat. Fresh haemorrhage may be present even in these regenerating tubules

The interstitial tissue at 4 to 6 days has a fibrillary oedematous appearance, and is considerably increased in amount. It contains endothelial nuclei and some large mononuclear cells and fibroblasts, but no polymorphs.

It will be appreciated that the appearances at this stage are indistinguishable from those of the repaired proximal convoluted tubule necrosis in neighbouring parts of the cortex.

ZONE OF PARTIAL SURVIVAL (Fig 46)

At about 5 days these repair processes spread into the zone of partial survival The regeneration of the proximal convoluted tubules here is delayed as compared with that in the live margin zone. The other tubules which had remained intact in this area (viz. the distal convoluted tubules and the cortical segments of the collecting tubules) appear healthy, with good leptochromatic nuclei and basophil cytoplasm. In some of these tubules the epithelium appears to be proliferating, and there are numerous nuclei packed closely side by side.

The specific case of the cortex immediately beneath the renal capsule requires mention. As in the case of proximal convoluted tubule necrosis, the cortical necrosis may extend practically to the capsule. The subcapsular region is then a zone of partial survival, and repair processes are seen there at 5 days. The regenerated tissue which is thus formed can be distinguished easily from the shallow islets of normal live parenchyma left undamaged by the original necrosis

In the zone of partial survival, the glomeruli show repair processes from about 5 days onwards. The necrosed tuft shrinks down to a small rounded mass of structureless debris, over whose surface there is a proliferation of

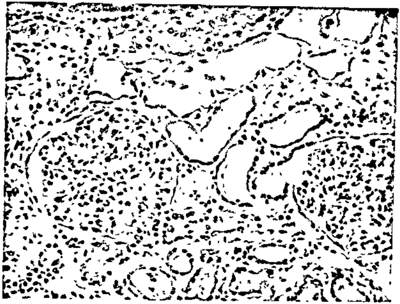


FIG 45 Healing stage of live margin zone of gross R C N.. Much regeneration of proximal convoluted tubules with interstitial oedema Glomeruli and distal convoluted tubules have survived 8½ days after U P A



FIG. 46 Healing stage of zone of partial survival in focal R C N Poor regeneration of proximal convoluted tubules The glomeruli show various degrees of damage but have some epithelial proliferation.
6 days after U.P A



FIG. 47 Epithelial proliferation over necrosed glomerulus in zone of partial survival of gross R.C.N., 9 days after U.P.A.



FIG. 48. Scarred glomeruli in the late stage of patchy R.C.N. They indicate the original site of the zone of partial survival. 4 weeks after U.P.A.

epithelial cells (Fig. 47). At the same time, a few spindle-shaped nuclei penetrate from the stalk into the necrosed centre of the tuft. At 10 to 15 days the tuft is represented by this mass of amorphous material, which contains occasional fibroblasts and is completely covered by a layer of regenerated cubical epithelium. During the next few weeks the glomerulus gradually shrinks The original site of the partial survival zone can then be recognised by the row of scarred glomeruli of this type, in contrast to the undistorted dead glomeruli of the zones internal to this (Fig. 48).

In those particular glomeruli where only half of the tuft was necrosed, this half undergoes the same changes that have just been described. The half which was not involved by the original necrosis remains quite unaffected, and does not show any reactive change. In the outer part of the zone, certain glomeruli, which had been only slightly damaged, recover almost completely and finally have merely a few adhesions to the capsule

PERIPHERAL DEAD ZONE (Fig. 49)

From 7 days onwards, there is a gradual extension of the repair process into the peripheral dead zone. Regeneration of the tubular epithelium is very poor; most of the dead tubules disappear completely, leaving the oedematous intertubular stroma in which can be seen the old capillary spaces and scattered fibroblasts and monocytes. In this tissue there are a few dilated tubules with low basophil epithelium which are probably regenerating distal convoluted tubules. There are also scattered narrow tubules or islets of epithelium which appear to result from the atrophy of these regenerated tubules The proximal convoluted tubules do not appear to regenerate here. Certain capillaries in this area become large and sinusoidal and are rather congested; this appearance is seen particularly under the renal capsule. Occasional endothelial cells may be seen spreading along the intertubular capillaries, but there is no regeneration of endothelium in the arteries.

Internal to the advancing edge of this repair, a zone of re-establishment of circulation in the dead tissue is evident at 15 days, and can be seen for some weeks later Fresh red corpuscles are present in large amount in many of the glomeruli, and in lesser amount in a few of the neighbouring capillaries and in the lumen of some of the dead arteries. This blood appears to be in free, though not necessarily very active, circulation from the neighbouring live tissue. Thrombosis does not occur. The new circulation is particularly obvious in the glomeruli which, though dead for 2 weeks or more, retain their general structure very well (in contrast to the destruction of glomeruli in the zone of partial survival). Their capillary loops are normally patent and distinct from each other, but they have no endothelium or epithelium remaining, have no nuclei at all, and appear to consist merely of intact dead basement membrane. Nevertheless many of them are filled by quite fresh blood with



FIG. 49 Healing stage of peripheral dead zone of gross R.C.N. Some fresh blood is entering the area, and the intertubular capillaries show new endothelium. A little tubular repair is present. 8½ days after U.P.A.



FIG. 50 Re-establishment of circulation through a long dead glomerulus in late stage of peripheral dead zone in patchy R.C.N. 4 weeks after U.P.A.

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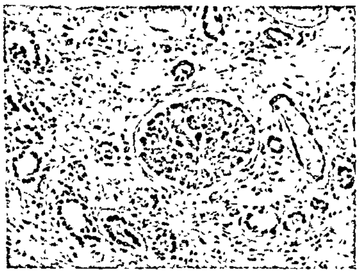


FIG. 50 Re-establishment of circulation through a long dead glomerulus in late stage of peripheral dead zone in patchy R.C.N. 4 weeks after U.P.A.

normally staining red corpuscles, and they seem to be functioning very well as vascular channels (Fig. 50). It is of interest that precisely the same re-establishment of circulation in dead glomeruli lying in completely dead parenchyma is seen near the edge of ordinary infarcts which are some weeks old.

FINAL STAGES

Only three examples of the late stage of R.C.N. have been studied. Case 70 of the present series shows the appearances of confluent focal R.C.N. at 34 days; this has no arterial lesions. Dr. Grasby has kindly allowed us to examine slides of his Case 2 (1947) of patchy R.C.N. at 30 days, and we have also had the privilege of seeing the slides of the case of patchy R.C.N. at 28 days described by *Joekes and Bull* (1948).

The process of repair described in the last section continues to encroach on the dead tissue at the centre during the third, fourth and fifth weeks. By the

At the site of the original partial survival zone, the scarred glomeruli show little alteration from what was seen at 15 days; they remain as fibrous masses covered by epithelium The glomerular capsule does not show any alteration or thickening of its basement membrane. A moderate number of regenerated tubules are present here; they are rather small and are lined by a low basophil epithelium containing many nuclei. These tubules are separated by a considerable amount of connective tissue made up of condensed stroma and new fibrous tissue.

Internal to this zone, there is a layer representing the peripheral dead zone, the polymorph zone and the outer part of the centre dead area. Here the glomeruli remain as intact ghosts, sometimes containing fresh red corpuscles indicative of a re-established circulation In a few of these glomeruli, occasional fusiform nuclei are migrating into the tuft. The remainder of the parenchyma is replaced by loose connective tissue, in which the remains of a few necrotic tubules can be seen. A small number of large regenerated tubules are also present here. These have a well-formed cubical epithelium which is lightly eosinophil and has a sharp luminal surface; the nuclei are closely packed at the base of this epithelium. Fresh blood is present in a number of the capillaries. This zone of repair reaches a thickness of about 1 mm. within 4 or 5 weeks; the thickness being measured from the line of scarred glomeruli to the edge of the remaining dead tissue in the centre.

In the outer part of the remaining dead tissue at the centre, endothelial nuclei are migrating along the original intertubular capillaries The large multinucleated tubules, which were a prominent feature of the organised layer, also extend in places into the outer part of the remaining centre dead

area. Occasionally it can be seen that these large tubules are giving rise to a low epithelium which is spreading to reline old necrosed tubules. Where this happens, the debris of the dead epithelium is changed to small eosinophil fragments. There is still an area of quite unaltered necrosed cortex remaining at the centre, its size depending on that of the original mass of necrosis.

Clearly this repair process is identical with that which occurs in the repair of an ordinary infarct of the kidney. The layer of connective tissue is formed at the expense of the dead tissue; it is not a fibrosing reaction in the surrounding parenchyma.

Calcification. Certain authors have recorded the calcification of tubules and sometimes of glomeruli in the neighbourhood of areas of R.C.N., at various times from 5½ days to 18 days after the onset of the necrosis (Klotz, 1908; Jardine and Teacher, 1911, Case 1; Geipel, 1925; Scriver and Oertel, 1930, Case 1; Wolfson, 1932; Kellar and Arnott, 1933, Cases 1 and 3; Ash, 1933, Case 1). This is quite an authentic lesion, but it is uncommon and has not been seen in the present series. In Case 2 of Grasby (1947) it involves the remaining dead tissue which lies in the subcapsular zone of organisation of the necrosed area; there is little calcification in the juxtamedullary part.

SUBSEQUENT VASCULAR REACTIONS NEAR THE MARGIN

The subjects to be discussed in this section are the organisation of the arterial thrombi in the repairing zones, the development of a fibrinoid change in the arteries of the live margin zone, and a proliferative capsulitis which sometimes occurs in glomeruli there.

ORGANISATION OF OCCLUSIVE THROMBUS IN LARGE ARTERIES

Repair begins at the lower end of the main thrombus in the intralobular artery at 6 days, i.e. at about the time when regeneration is occurring in the tissues around. A few endothelial cells appear, lining small clefts in the proximal end of the thrombus (Fig. 51). This is seen in every case of the present series after 6½ days. By about 10 to 15 days the organisation has led to the replacement of most of this part of the thrombus by a loose connective tissue. At the

margin and partial survival zones is thus filled by a loose cellular connective tissue which has been recanalized by a few large capillary sinuses. The proximal end of this tissue is derived from the endarteritis obliterans, and the distal part is derived from the organisation of the solid occlusive



FIG 51 Endothelial proliferation into solid occlusive thrombus in trunk of intralobular artery, in gross R C.N. 8½ days after U.P.A.

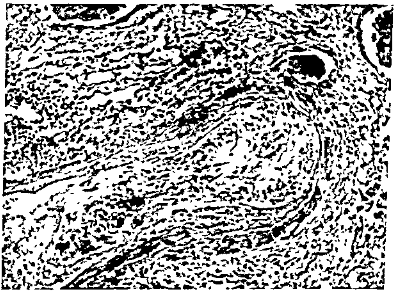


FIG 52 Organisation of solid occlusive thrombus in a large intralobular artery in gross R C N. Much proliferation of intima proximally. 15 days after U.P.A

thrombus, but at this stage there is no morphological difference between the tissue of the two parts. The media of the artery shows a gradual transition from apparent normality in the live margin zone to a thin fibrillary structure with occasional nuclei in the zone of partial survival.

The distal segment of the artery shows a remarkable absence of repair in the peripheral dead zone or in the outer part of the centre dead area. It remains as a completely necrotic ghost running through the broad band of regenerating tubules and organisation which is spreading into the centre dead area. No new endothelium can be observed in it even as late as 30 days, rarely there are a few flat nuclei on the outer surface of the dead media, but these are presumably derived from the surrounding connective tissue. The mural thrombus which had originally been formed in this segment of the artery remains unaltered Nevertheless there is certainly some circulation of blood through these dead arteries, as shown by the fact that they contain quite fresh red corpuscles. This blood clearly comes through the recanalised endarteritis. The continuance of circulation without any new formation of thrombi in these long-dead arteries which have no endothelium is the same phenomenon as was observed in the dead glomeruli in the region.

In the literature, organisation of the occlusive thrombus and obliterative endarteritis at this site have been recorded at 7 days (Glynn and Briggs, 1914; Stoeckenius, 1921; Geipel, 1925), at 9 to 11 days (Westman, 1928, Case 1; Scriver and Oertel, 1930, Case 1; Dalrymple, 1930; Zalka, 1933, Case 1, Davis, 1940 and 1949, Case 1), and later (Wolfson, 1932; Gáspár, 1938, Azevedo and Teixeira, 1938; Stening, 1939).

MEDIAL DEGENERATION

This process is a fibrinous or fibrinoid degeneration in arteries of the live margin zone or outer part of the zone of partial survival It is most prominent in thrombosed arteries, and affects the entire thickness of the arterial wall over much or all of its circumference, particularly at the site where the occlusive thrombus is most firmly adherent (Fig 53). When this change occurs, the arterial wall develops precisely the same structureless appearance as the thrombus and, as there is no line of demarcation between the two, it g[illegible]

a [illegible]

[illegible]

non-thrombosed arteries in the live margin zone around the area of R.C.N., even in cases of focal R.C.N. In these arteries and arterioles it involves the entire circumference and length of the vessel, replacing the whole media but leaving the intima intact (Fig. 55). The lumen of these vessels is narrowed but remains

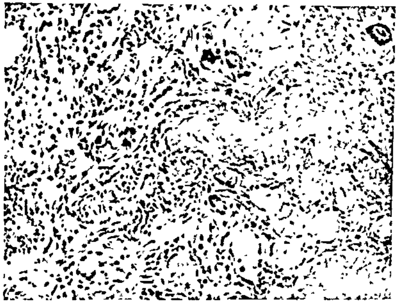


FIG 53 Medial degeneration of artery in partial survival zone of patchy R C N Normal artery on left, passing into thrombosed dilated portion on right This thrombosed portion shows severe medial degeneration 7½ days after U P A



FIG 54 Medial degeneration in a thrombosed artery in the partial survival zone of gross R C N The thrombus and media are fused to a homogeneous mass 10 days after U P A



FIG 55 Medial degeneration of an afferent arteriole which has not been thrombosed, in partial survival zone of gross R C N 8½ days after U P.A.

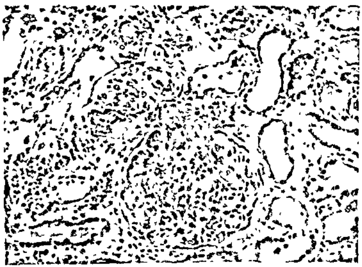


FIG 56 Medial degeneration spreading along stalk afferent vessel, in live margin zone of gross R C N. 8½ days after U P A

open. The change sometimes reaches into the stalk afferent vessel, whose wall then becomes a thick eosinophil structure with a patent lumen lined by apparently normal endothelium (Fig. 56). In a few cases the process extends out into the capillary loops of the glomeruli or even along the capsular basement membrane. There is never any inflammatory reaction around the affected vessels

Soon after this fibrinoid change has occurred in the wall of the original thrombosed artery, there is irruption of fibroblasts into it from the surrounding interstitial tissue The entire mass is broken up quickly into small eosinophil fragments lying between spokes of cellular fibrosis; at about 10 to 15 days it is represented only by a star of loose granulation tissue. The same organisation also occurs in some of the arterioles which have undergone the fibrinoid change.

This lesion has been described or illustrated by various authors in cases of R.C.N with a duration of 5 to 17 days (Griffith and Herringham, 1906; Scriver and Oertel, 1930, Case 1; Ash, 1933, Case 1; Gáspár, 1938; French, 1940; Hugin, 1946, Case 1; Donnelly and Thomas, 1946, and Mauzy and Donnelly, 1949; Smith and Muirhead, 1951, Case 1).

PROLIFERATIVE CAPSULITIS

In certain kidneys at 7 to 10 days, some of the glomeruli of the live margin zone show a proliferation of the capsular epithelium (Fig. 57). Even in the earliest stages of this proliferation, the glomerular space is otherwise empty; there is never any evidence that there has been colloid or other protein or blood in this space. Subsequently the proliferation proceeds to the formation of typical epithelial crescents (Fig. 58). None of the patients had lived long enough to develop fibrosis of the crescent. Proliferative capsulitis may be seen in a glomerulus whose tuft and capsular basement membrane show the fibrinoid change which has been described above; there is insufficient evidence to determine whether these two processes are intimately related or merely coincidental marginal phenomena.

The capsulitis was observed particularly in one case where there was a continuous hypertension during the puerperium, but lesser degrees of it were seen in 7 other patients, of whom 2 had slightly raised blood pressures and 2 had rather low blood pressures in the puerperium. The condition therefore appears to be a purely local reaction in glomeruli around areas of R.C.N.

In the literature, proliferative capsulitis near the margin of the dead area has been recorded in cases of R.C.N as early as 5 days (Davidson and Turner, 1930, Case 4; Dunn and Montgomery, 1941, Case 6; Puumala and Wells, 1944; Smith and Muirhead, 1951, Case 1), and in later cases (Gareiss-Dollitzsturm, 1928; Scriver and Oertel, 1930, Case 1; Dalrymple, 1930; Azevedo and Teixeira, 1938; Lieu, 1938; Hunt, 1939; Dunn and Montgomery, 1941, Cases 6 and 8; Sheldon and Hertig, 1942, Case 1; Campbell and Henderson, 1949, Case 3).



FIG. 57 Slight proliferation of capsular epithelium of glomerulus, in live margin zone of gross R.C.N. 8½ days after U.P.A.

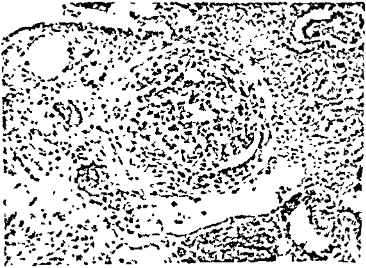


FIG. 58 Epithelial crescent formation in partial survival zone of patchy R.C.N. 7½ days after U.P.A.

external haemorrhage, a stillborn baby, retroplacental clot, and subserosal haemorrhages over the uterus. In other cases there is only a very incomplete obstetric record, and it is impossible to determine whether U.P.A. had occurred. This applies particularly to cases reported simply as "eclampsia". Nevertheless, the occurrence of premature stillbirth in a toxaemic multipara is certainly suggestive of an unnoted U.P.A., especially when is it followed by R.C N.

Hugin (1946, Case 2). Age 29, para 1, gestation 33 weeks, duration 5 days U P.A. followed by eclamptic convulsions Anuria to death.

Adam (1945, Case 6). Age 28, para 1, gestation unknown, duration 9 days. U.P A. Oliguria, with late rapid increase of urine output.

Bryce-Smith et al. (1949). Age 21, para 1, gestation 35 weeks, duration 13 days. No obstetric history, but *extensive uterine haemorrhages at autopsy.* Oliguria for first week.

Donnelly and Thomas (1946) (also reported by Mauzy and Donnelly, 1949, Case 1). Age 42, para 6, gestation 31 weeks, duration 13 days. U.P.A followed by severe oliguria. Biopsy was performed at 55 hours *after the accidental haemorrhage*, and showed extensive necrosis of the epithelium of convoluted tubules, which was reduced to pinkish granular debris. The capillary loops of scattered glomeruli were dilated and filled with granular material, and some loops were necrosed. The arterioles presented no histological abnormality. The patient died at 13 days. The kidney then showed lesions which are interpreted in the present paper as the healing stage of a focal R C.N.. An occasional necrosed glomerulus was seen, and there was necrosis of some arterioles and glomerular loops. The proximal convoluted tubules were dilated and showed epithelial regeneration. There were granular casts in many collecting tubules.

Crook (1926). Age 29, para 1, gestation 34 weeks, recovered No note about U P.A.. Severe oliguria Biopsy was performed on the 5th day and showed a focal R.C.N.. There was a healing proximal convoluted tubule necrosis with some polymorph infiltration, but in the tissue examined there were two areas of focal R C.N., each less than 1 mm in diameter [illegible]
of stalk afferent vessels. [illegible]
tubules in these foci [illegible]
interstitial tissue remained alive. This patient slowly developed a better urinary output, and finally recovered.

MINOR RENAL CORTICAL NECROSIS

The lesions which characterise this group are small scattered areas of necrosis, mainly in the outer half of the cortex, and varying up to 2 or 3 mm. in diameter. These areas have a centre made up of peripheral dead zone, usually with a rather diffuse polymorph infiltration. Around this are the zones of partial survival and of live margin.

The arterial changes are present at 14 to 18 hours. They consist of (*a*) dilatation and solid occlusive thrombosis of the small distal segments of the intralobular arteries and of the afferent arterioles in the areas, (*b*) necrosis of the

affected portions of the arterial tree, usually with red corpuscles or leucocytes in the media. There are no lesions in the main intralobular arteries. The remainder of the cortex always shows an extensive proximal convoluted tubule necrosis, sometimes associated with benign glomerular thrombosis.

[illegible] general to those of focal R C.N. but [illegible] are a variable number of small sur[illegible] recognisable to the naked eye. These areas have whitish centres and congested margins (Fig 60).



Fig 60 Kidneys showing minor R.C.N (½ natural size).

CASE NOTES

Three cases of the present series fall into this group

Case 48. Age 26, para 1, gestation 38 weeks, duration 2 days. Complete anuria after U P A. One convulsion shortly before delivery Delivered at 47 hours, and died in coma 1 hour p p

Case 49 Age 24, para 2, gestation 32 weeks, duration 3 days Some external haemorrhage Delivered at 15 hours Complete anuria after delivery One convulsion next day, and died in coma 5½ hours p.p

Case 50. Age 28, para 5, gestation 33 weeks, duration 9 days. External haemorrhage 1 day before delivery Developed puerperal pyrexia and died 9 days p.p.

LITERATURE

Bowes (1934). Age 32, para 2, gestation 31 weeks, duration 4 days. Stillbirth but no obstetric details Severe oliguria.

Portes (1935, Case 6) Age 32, para 2, gestation 31 weeks, duration 5 days U.P.A followed by severe oliguria

Poten (1906). Age 26, para 1, gestation 31 weeks, duration $5\frac{1}{4}$ days. U.P.A. *followed* by oliguria.

Lowrie and O'Connell (1950). Age 36, para 14, gestation 26 weeks, duration 7 days. U.P.A. followed by oliguria. Renal lesions very widespread.

Beneke (1894). Brief note. Died 10 days after eclampsia. No obstetric details.

PATCHY RENAL CORTICAL NECROSIS

In this group there are multiple rather large patches of R.C.N., which destroy about one-third to two-thirds of the cortex. The individual lesions vary considerably in size, but many are large enough to show a centre dead area with the complete series of zones around it. The remaining tissue shows various grades of damage to proximal convoluted tubules, and there may be benign glomerular thrombosis. The juxtamedullary nephrons are relatively unaffected

The characteristic arterial lesion in the developed case is the formation of thrombus in the intralobular arteries about midway along their course in the cortex The proximal end is a short solid thrombus. The remainder is of trellis type, which distally develops a central lumen and gradually opens out to continue as a thick mural thrombus for some distance up the arterial tree. All this distal part of the arterial tree is necrosed and dilated Towards its periphery it may contain some thin mural thrombus, and there may be fibrin plastering of dilated stalk afferent vessels, but this is not a prominent feature. Basophil intimitis is very uncommon. Arterial lesions are not seen *before 36 hours, but are present in all cases after that time.*

To the naked eye, the kidney during the first day shows a broad pale cortex with patchy areas of congestion. In the later cases the kidneys are enlarged (mean weight 245 gm), and have very numerous patches of obvious cortical necrosis, chiefly in the outer part of the cortex (Fig. 61). In the remaining parts of the cortex, there are multiple petechial haemorrhages on a congested background. In some kidneys, the entire cortex seems to consist of confluent haemorrhagic streaks in which there are small areas of white necrotic tissue (Fig. 62). The columns of Bertini are relatively unaffected in most cases

These cases of patchy R.C.N raise a point of some interest in connection with the arterial supply to the kidney as a whole. In patchy and in minor R.C.N., there is a tendency for the necrosis to be much more extensive in the mesial part of the kidney immediately above and below the renal pelvis (Figs. 60 and 62). In these regions the condition may be that of a gross R C.N., though the lesions along the convexity of the kidney are relatively small. There has [illegible] R C.N within [illegible] ney [illegible] sed

areas of the columns of Bertini even more quickly than in the hilar region.



FIG. 61 Kidneys showing mild and severe grades of patchy R.C.N. (½ natural size)



FIG. 62 Kidneys showing the streaky type of patchy R.C.N. (½ natural size)

CASE NOTES

There are 8 late cases of patchy R.C.N. in the present series.

CASE 51. Age 20, para 3, gestation 38 weeks, duration 2½ days. Developed eclampsia and, four hours later, U.P.A. Seven convulsions before delivery at 3 hours. Two convulsions soon after delivery. Died after coma of varying depth 2¼ days p.p. Details of urine output are given in the subsequent clinical section.

CASE 52. Age 41, para 13, gestation 26 weeks, duration 5 days. Accidental haemorrhage also in twelfth pregnancy. Severe oliguria with maximum urine output of 180 cc. on third day.

CASE 53. Age 35, para 2, gestation 34 weeks, duration 6½ days. Oedema for 2 weeks previously. Delivered at 9 hours. Subsequent severe oliguria; maximum urine output 60 cc. per day.

CASE 54. Age 41, para 5, gestation 33 weeks, duration 6½ days. Oedema for 3 weeks previously. Some external haemorrhage. Delivered at 30 hours. Subsequent urine output never over 100 cc. Heart 400 gm.

CASE 55. Age 40, para 10, gestation 33 weeks, duration 7½ days. Some external haemorrhage. Delivered at 12 hours. Urine output 300 cc. per day for 3 days, and then complete anuria. Sudden terminal collapse. Heart 390 gm.

CASE 56. Age 34, para 3, gestation 24 weeks, duration 10 days. Some external haemorrhage. Almost complete anuria afterwards.

CASE 57. Age 43, para 4, gestation 34 weeks, duration 10½ days. Severe external haemorrhage. Delivered at 9 hours. Subsequent urine output about 200 cc. per day. Given much hypertonic glucose intravenously. Sudden terminal collapse with irregular pulse.

CASE 58. Age 32, para 7, gestation 30 weeks, duration 11½ days. Slight external haemorrhage. Delivered at 15 hours. Severe oliguria for 4 days subsequently, improving to about 800 cc. per day. Sudden terminal collapse.

LITERATURE

Ivens (1922). Age 23, para 1, gestation 32 weeks, duration 2½ days. U.P.A. 1½ days before delivery.

Couvelaire (1912, Case 2). Age 23, para 1, gestation 31 weeks, duration 2½ days. U.P.A. and eclampsia.

Jardine and Kennedy (1913, Case 2). (Also recorded by Jardine and Kennedy, 1920, Case 8.) Age 38, para 2, gestation 40 weeks, duration 2½ days. Twins born alive. No mention of U.P.A.

Spickmann (1934, Case 3). Pre-eclampsia. No obstetric details. Died 2½ days p.p.

Evans and Gilbert (1936). Age 39, para 8, gestation 31 weeks, duration 3 days. Eclampsia. No obstetric details, but subserosal haemorrhages over uterus.

Cutler (1895). Age 23, para 1, gestation unknown, duration 4 days. Eclampsia. No mention of U.P.A.

O'Sullivan and Spitzer (1946, Case 3). Age 45, para 11, gestation 24 weeks, duration 4 days. U.P.A.; severe oliguria.

Cortese (1935). Age 23, para 1, gestation 31 weeks, duration 5 days. U.P.A.; almost anuria.

de Snoo (1936, Case 4). Age 40, para 8, gestation 30 weeks, duration 5 days. U.P.A.; oliguria. Hypertrophy of heart.

Smith and Muirhead (1951, Case 1). Age 29, para 4, gestation 31 weeks, duration 5 days. U.P.A. and eclampsia.

Jardine and Teacher (1911, Case 1). (Also described by Jardine, 1906; Teacher, 1908, Case 1; Jardine and Teacher, 1910, Case 1; Jardine and Kennedy, 1920, Case 5). Age 36, para 7, gestation 31 weeks, duration 5½ days. Eclampsia. Stillbirth. No obstetric data or description of uterus.

Donnack and Walker (1946). Age 31, para 3, gestation 31 weeks, duration 5½ days. U.P.A. Severe oliguria.

Davidson and Turner (1930, Case 4). Age 33, para 6, gestation unknown, duration over 5 days. Pre-eclampsia. Stillbirth but no obstetric details.

MacGillivray (1951, Case 7). Age 28, para 1, gestation unknown, duration 6 days. U.P.A.

Warner and Hibbitts (1932) Age 26, para 1, gestation 26 weeks, duration 6½ days U.P.A. 3½ days before delivery

Sheldon and Hertig (1942, Case 1). Age 33, para 5, gestation 33 weeks, duration 7 days. U.P.A., severe oliguria

Scriver (1935, Case 4). Age unknown, para 1, gestation 31 weeks, duration 7 days. U.P.A., anuria

Kellar and Arnott (1933, Case 3). Age 29, para 3, gestation 23 weeks, duration 7 days U.P.A.; almost anuria.

Cruickshank (1923). Age 23, para 10, gestation 22 weeks, duration 8 days. U.P.A., anuria

Scriver and Oertel (1930, Case 1). (Also recorded by Scriver, 1935, Case 1) Age 34, para 15, gestation 27 weeks, duration 9 days. Stillbirth and gross retroplacental clot

Grasby (1947, Case 1). Age 15, para 1, gestation 31 weeks, duration 9 days U.P.A. followed by severe oliguria.

Scriver (1935, Case 5). Age 30, para 4, *gestation 31 weeks*, duration 10 days. U.P.A., oliguria

Davidson and Turner (1930, Case 2). Age 39, para 4, gestation 31 weeks, duration 10½ days Stillbirth No obstetric data.

Lloyd (1906) Age 39, para 7, gestation 37 weeks, duration 11 days U.P.A., post-partum eclampsia

Sheldon and Hertig (1942, Case 2). Age 40, para 4, gestation 31 weeks, duration 11 days U.P.A., almost anuria.

Manley and Kliman (1927). Age 38, para 1, gestation 35 weeks, duration 12 days U.P.A., oliguria.

Davidson and Turner (1930, Case 1). Age 37, para 5, *gestation 28 weeks, duration* 12½ days Stillbirth and accidental haemorrhage.

Wolfson (1932) Age 35, para 6, gestation 27 weeks, duration over 10 days. Accidental haemorrhage Heart 550 gm

Joekes and Bull (1948) Age 24, parity unknown, gestation 29 weeks, duration 28 days U.P.A. Treated by artificial kidney

Grasby (1947, Case 2) Age 40, para 5, gestation 31 weeks, duration 30 days U.P.A. Late diuresis.

GROSS RENAL CORTICAL NECROSIS

This group includes the cases in which there is almost total destruction of the renal cortex, the only parts which are not involved are a few juxtamedullary and subcapsular nephrons, and an occasional band of tissue radiating from the intermediate zone out to the capsule. In these radial bands there are

sometimes vessels running from the intermediate zone to unite with the vessels of the capsule; they are prominent because of their dilatation. These areas which are not involved in full R.C.N. show various grades of glomerular and tubular damage and, in fact, much of the tissue consists of live margin and partial survival zones.

In Case 61 there were, in addition to the cortical lesions, tongues of necrosis about 2 to 3 mm. in diameter running down from the necrosed cortex through the intermediate zone into the outer part of the medulla. This condition has also been noted by Scriver and Oertel (1930, Case 2) and Lowrie and O'Connell (1950). In some reports in the literature, such an extension into the medulla has been diagnosed in cases which seem to have been really pyelonephritic lesions in the medulla, or infarction of the medulla due to thrombosis of the renal vein

The great mass of the cortex consists of centre dead area, framed by the various zones previously described. The proximal end of the damage to the intralobular artery is at the junction of the live margin zone with the zone of partial survival, just above the juxtamedullary region. Here the artery suddenly becomes dilated and its lumen is occluded by solid thrombus. The media at this point is rather fatty but its nuclei appear healthy. At the junction of the zone of partial survival with the peripheral dead zone, the arterial walls are clearly necrosed; the solid thrombus may cease abruptly or may gradually merge into trellis thrombus which continues about as far as the polymorph zone. The whole length of the solid and trellis thrombus is thus about 500 microns. More distally, the entire arterial tree is necrosed and dilated, and shows extensive thin mural thrombosis throughout; this continues, to form a plaster thrombus in nearly all the stalk afferent vessels. Basophil intimitis is usually present. The trellis and thin mural thrombi and the basophil intimitis are seen at 36 hours, but the solid occlusive thrombus probably does not develop until about 3½ to 5 days.

In one single case of gross R C N. at 10 days in the present series, the vascular lesions were different from those described above. This case, though unusual, is of considerable aetiological importance. The necrosis of parenchyma and the formation of the marginal zones was of the usual type. The solid occlusive thrombus was present near the origin of the intralobular arteries *However, though the distal part of the arterial tree in the area of* R C N. was dead, it was not greatly dilated and it did not show thrombosis of any type at all. A similar appearance may be seen in small segments of the cortex in other kidneys with gross R.C.N.. This point will be discussed later.

Macroscopically, the kidney is always enlarged (mean weight 230 gm.). At 8 to 14 hours it is pale or rather congested, sometimes with punctate haemorrhages. At 36 to 50 hours it is intensely congested, and has a deep damson colour with thin paler bands radiating out through the cortex. There

are subcapsular and juxtamedullary areas of haemorrhage or congestion At 5 to 15 days the kidney shows the typical appearance of gross R.C.N. affecting the entire depth of the cortex (Fig. 63). The necrosed cortex is now of an opaque whitish-yellow colour, and is surrounded by a continuous irregular red margin under the capsule and in the intermediate zone. This red margin is much less prominent in the later cases. At various places there are radiating bands, sometimes narrow and sometimes rather broad, of congested tissue coursing across the cortex from the intermediate zone out to the capsule. On the surface of the kidney these form reddish and apparently depressed areas suggesting old scars These areas are not in fact shrunken; they are really at their original level, but the surrounding surface is raised because of the swelling of the necrosed cortex

The columns of Bertini are usually involved as severely as the remainder of the cortex.

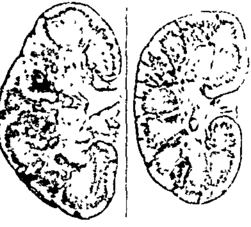


FIG 63 Kidneys showing classical gross R C N (½ natural size)

CASE NOTES

There are 9 late cases of gross R C N in the present series

CASE 59. Age 37, para 9, gestation 29 weeks, duration 2 days Oedema and dyspnoea for 3 weeks previously Version, followed 3 hours later by U P A. Delivered at 19 hours. Died 29 hours p p Eclamptic lesions of liver.

CASE 60 Age 39, para 5, gestation 38 weeks, duration 2 days Ante-partum eclampsia. Delivered at 20 hours Died in coma 28 hours p p Heart 460 gm Urine output 400 cc on each day

CASE 61 Age 27, para 2, gestation 25 weeks, duration 5 days. Some external haemorrhage. Delivered at 7 hours Sudden collapse followed by coma. Died 4¾ days p.p.

CASE 62. Age 34, para 7, gestation 38 weeks, duration 5½ days. Pre-eclampsia for

3 days previously. U P.A. during labour. Delivered at 2 hours Urine output 50 cc per day.

CASE 63. Age 31, para 3. gestation 31 weeks, duration 6½ days. Some oedema for one month previously. Severe external haemorrhage. Delivered at 8 hours. Anuria for 3 days, with improvement to 400 cc. urine on last day.

CASE 64. Age 38, para 3, gestation 28 weeks, duration 8½ days Severe external haemorrhage. Delivered at 8 hours. Renal denervation and biopsy at 36 hours. Daily urine output never exceeded 48 cc.

CASE 65. Age 33, para 4, gestation 22 weeks, duration 9 days. Delivered at 17 hours. Almost complete anuria thereafter.

CASE 66. Age 30, para 5, gestation 39 weeks, duration 10 days. Pre-eclampsia for 2 weeks previously U.P.A. during labour. 30 cc. urine on first day p p; complete anuria thereafter. Terminal convulsion. One healing eclamptic lesion found in liver.

CASE 67. Age 34, para 10, gestation 24 weeks, duration 15 days. Severe oliguria and persistent vomiting after delivery. Convulsions from 11 to 13 days p.p. Died in coma 15 days p.p

LITERATURE

Baird and Dunn (1933, Case 11). Age 29, para 3, gestation unknown, duration 2¼ days. Eclampsia; no obstetric data.

Herzog (1913, Case 3). Age 22, para 1, gestation premature, duration 3¼ days. Eclampsia. No haemorrhages over uterus.

Jardine and Kennedy (1913, Case 1). (Also recorded by Jardine and Kennedy, 1920, Case 7). Age 34, para 9, gestation 31 weeks, duration 4½ days. U.P.A. followed by complete anuria

Reyna (1936). Age 39, para 8, *gestation 27 weeks, duration 4½ days.* U.P.A . *Hyper*trophy of left ventricle.

Geipel (1914). Age 32, para 3, gestation 31 weeks, duration 4½ days. U.P.A. followed by complete anuria.

Bruno (1941). Age 35, para 2, gestation 27 weeks, duration 4½ days. No obstetric data, but uterine haemorrhages at autopsy.

Davis (1949, Case 3). Age 29, para 3, gestation 35 weeks, duration over 4 days. U.P.A . Biopsy 4 days later showed R C.N with thrombosis of practically all arterioles. The medullary tissue was viable.

Puumala and Wells (1944). Age 49, para 9, gestation 40 weeks, duration 5 days. Pre-eclampsia; live baby. Complete anuria.

Jardine and Kennedy (1920, Case 10). Age 48, para 7, gestation unknown, duration 5½ days. No obstetric data. Post-partum eclampsia.

Stroink (1934, Case 2). (Also recorded by de Snoo, 1936, Case 3). Age 36, para 5, gestation 36 weeks, duration 5½ days. U.P.A.. Hypertrophy of heart.

Schüppel (1914). Age 35, parity unknown, gestation 31 weeks, duration about 5 days. No obstetric data.

Vilk (1938). Age 25, para 2, gestation 36 weeks, duration 6 days Stillbirth; no obstetric data.

Davis (1949, Case 2). Age 36, para 6, gestation 35 weeks, duration 6 days. Eclampsia and U.P.A.

Carson and Rockwood (1926). Age 36, para 7, gestation 27 weeks, duration 6 days. Stillbirth; no obstetric data.

MacGillivray (1950, Case 1). Age 41, para 15, gestation unknown, duration 6½ days Pre-eclampsia and U.P.A.

Pritzker and Rose (1945) Age 28, para 4, gestation unknown, duration 7 days. Stillbirth; no obstetric data.

Hugin (1946, Case 1). Age 35, para 6, gestation 37 weeks, duration 7 days. Pre-eclampsia and U P A.

Glynn and Briggs (1914) Age 29, para 1, gestation 35 weeks, duration 7 days U.P.A.. Almost anuria.

Geipel (1925). Age 35, para 2, gestation unknown, duration 7 days Stillbirth, no obstetric data One eclamptic convulsion.

Westman (1928, Case 1) (Also recorded by Bovin, 1927, Case 1) Age 29, para 2, gestation 35 weeks, duration 8 days. Pre-eclampsia and U.P A . Biopsy of kidney at [illegible]

[illegible] with much blood loss

Jardine and Teacher (1911, Case 2) (Also described by Teacher, 1908, Case 2, Jardine and Teacher, 1910, Case 2, Jardine and Kennedy, 1920, Case 6). Age 22, para 1, gestation unknown, duration 9 days Eclampsia Stillbirth, no obstetric data.

Hirst (1926, Case 1) Age 30, para 2, gestation 33 weeks, duration 9 days. Stillbirth, no obstetric data.

Scriver and Oertel (1930, Case 2). (Also recorded by Scriver, 1935, Case 2) Age 33, para 3, gestation unknown, duration 9 days U P A . Anuria subsequently

Griffith and Herringham (1906) Age 35, para over 5, gestation unknown, duration 10 days U P A . Some urine from third to fifth day.

Dalrymple (1930). Age 30, para 1, gestation 40 weeks, duration 11 days Placenta praevia Stillbirth. Eclampsia post partum.

Rolleston (1913) Age 48, para 13, gestation 42 weeks, duration 11 days Stillbirth, no obstetric data

Zaayer (1903) Age 30, para 6, gestation unknown, duration 11 days Stillbirth, no obstetric data.

Davis (1940). (Also recorded by Davis, 1949, Case 1) Age 24, para 1, gestation 36 weeks, duration 11 days. U.P A One eclamptic convulsion.

Stening (1939) Age 35, para 4, gestation 31 weeks, duration 15 days Eclampsia and U P A.

Gáspár (1938) Age 38, para 11, gestation unknown, duration 15 days Placenta praevia, stillbirth No uterine haemorrhages.

OTHER LITERATURE

There are a number of cases of R C.N of uncertain extent in patients who have had definite or possible U P.A . The clinical and pathological records in many of these cases are very scanty.

Lichtenstein (1912) A case following eclampsia.
Bates (1927) A case following pregnancy.
Kurzrock (1930) U P A Possibly a patchy R.C.N
Lindau (1932) Two cases in pregnancy toxaemia
Mansens (1933) Two cases following U P A
Johnstone (1933, Case 2) U P A
Navasquez (1935) recorded twelve cases in pregnancy but with no obstetric details
Rubin and Petru (1939) Two cases, one dying 7 days and the other 10 days p p.
Dunn and Montgomery (1941) mentioned seven cases of which six had U P.A.

3 days previously. U.P.A. during labour. Delivered at 2 hours. Urine output 50 cc. per day.

CASE 63. Age 31, para 3. gestation 31 weeks, duration 6½ days. Some oedema for one month previously. Severe external haemorrhage. Delivered at 8 hours. Anuria for 3 days, with improvement to 400 cc. urine on last day.

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Reyna (1936) Age 39, para 8, gestation 27 weeks, duration 4½ days. U P.A.. Hypertrophy of left ventricle.

Geipel (1914). Age 32, para 3, gestation 31 weeks, duration 4½ days. U.P.A followed by complete anuria.

Bruno (1941). Age 35, para 2, gestation 27 weeks, duration 4½ days. No obstetric data, but uterine haemorrhages at autopsy

Davis (1949, Case 3). Age 29, para 3, gestation 35 weeks, duration over 4 days. U.P A.. Biopsy 4 days later showed R.C.N with thrombosis of practically all arterioles. The medullary tissue was viable.

Puumala and Wells (1944) Age 49, para 9, gestation 40 weeks, duration 5 days. Pre-eclampsia, live baby. Complete anuria.

Jardine and Kennedy (1920, Case 10). Age 48, para 7, gestation unknown, duration 5½ days. No obstetric data Post-partum eclampsia.

Stroink (1934, Case 2). (Also recorded by de Snoo, 1936, Case 3). Age 36, para 5, gestation 36 weeks, duration 5½ days. U P.A.. Hypertrophy of heart.

Schuppel (1914) Age 35, parity unknown, gestation 31 weeks, duration about 5 days. No obstetric data.

Vilk (1938). Age 25, para 2, gestation 36 weeks, duration 6 days. Stillbirth; no obstetric data.

Davis (1949, Case 2). Age 36, para 6, gestation 35 weeks, duration 6 days. Eclampsia and U.P.A.

Carson and Rockwood (1926). Age 36, para 7, gestation 27 weeks, duration 6 days. Stillbirth; no obstetric data

MacGillivray (1950, Case 1). Age 41, para 15, gestation unknown, duration 6½ days. Pre-eclampsia and U.P.A.

CHAPTER X

RENAL CORTICAL NECROSIS NOT ASSOCIATED WITH ACCIDENTAL HAEMORRHAGE

Consideration has been given so far only to the cases of R.C.N which follow U.P.A.. However there are many cases of R.C.N. which are not a sequel to this obstetric complication, they may occur in males or non-pregnant females of any age, and they sometimes occur in obstetric cases where there has certainly been no U P A.

These cases of R C N. which are unrelated to U.P.A. fall into three general groups: children; abortions and certain other obstetric cases; adults and adolescents They show the same general pathological picture as the cases which follow U P.A There are a few typical cases of gross R.C N and a large number of cases of patchy R C.N., all of which show the typical arterial lesions The cases of focal R.C.N., on the other hand, are usually of a particular variety, in that the focal lesions tend to be in such large numbers that they become confluent.

CONFLUENT FOCAL R.C.N

The pathological appearances in this condition require description, because they are rather different from those of other types of R.C N , and have led to some confusion in the literature The characteristic features are (*a*) that there are very widespread lesions of glomeruli and tubules, (*b*) that this damage, however extensive, retains a nephronic distribution, (*c*) that the arteries are essentially unaffected

There are two broad types. In the common type, a single histological section of the cortex shows a great variety of appearances, each nephron shows lesions differing widely from those of its neighbours The differences are in the severity of the lesions and in their age, which may vary from about 6 hours up to 3 or 4 days old. Some proximal convoluted tubules are normal, others have colloid degeneration or hyaline droplet formation, and many show ordinary necrosis in various stages of development A few of the glomeruli are normal, some of them show gross congestion or stasis, some have benign thrombosis of capillary loops or stalk afferent vessels, others have solid adherent thrombi in these vessels, and many show partial or complete necrosis of the tuft Haemorrhage from some of these damaged glomeruli is present in the lumen of a variable number of proximal convoluted tubules The distal convoluted tubules and the interstitial tissues survive Thrombosis is seen in a few afferent arterioles, and very occasionally in small arteries There are never any lesions

Dieckmann (1942, Case 25). Pre-eclampsia but no obstetric data.
Dingle (1943, Case 1). Pre-eclampsia but no obstetric data.
McLetchie (1949, Cases 3 and 4). Eclampsia but no obstetric data.
Dodds (1949) Seven cases following U.P.A.
Miller (1949, Case 2) U.P.A.
Werner, Muckerman and Allen (1950, Case 4) Primipara with pre-eclampsia and stillbirth Possible minor R.C.N. at 2 days.
Crichton (1950) mentioned four cases following U.P.A.
MacGillivray (1950 and 1951) recorded eight cases of R.C N. in obstetric patients. His Cases 1 and 7 are included in the literature survey here, but the other cases are omitted as they form part of the series already studied in the present investigation.
Tennent and Starritt (1951) One case following U.P.A.
Priddle and Stevenson (1951, Case E.J) A case dying 58 days after U.P.A.

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These cases of R.C N which are unrelated to U.P A fall into three general groups: children; abortions and certain other obstetric cases; adults and adolescents They show the same general pathological picture as the cases which follow U P.A . There are a few typical cases of gross R.C.N and a large number of cases of patchy R.C.N , all of which show the typical arterial lesions The cases of focal R.C.N , on the other hand, are usually of a particular variety, in that the focal lesions tend to be in such large numbers that they become confluent

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in the main intralobular arteries. Thrombosis is sometimes seen in the veins, and may be a prominent feature.

The less common type of confluent focal R.C.N. *shows extensive lesions* with a more uniform appearance. The changes in the glomeruli and proximal convoluted tubules are in general similar to those in the former type; the main differences are (*a*) that the lesions appear to be all of about the same age, (*b*) that the lesions appear to be of greater severity. In some areas there is necrosis of distal convoluted tubules, dehaemoglobinisation of red corpuscles, and a slowing-down of the necrosis-changes in the proximal convoluted tubules The arteries are unaffected.

The repair stages of confluent focal R.C.N. are seldom described. As far as can be ascertained from the present material, the process of repair begins in numerous areas scattered throughout the cortex. The debris of the necrosed tubules is removed and the epithelium regenerates, but many of these reparied tubules subsequently atrophy. The necrosed glomeruli become replaced by fibrous tissue, and gradually disappear. Within a few weeks the whole area is replaced by a mass of connective tissue, made up of a condensation of the original stroma with the addition of some new fibrous tissue. In this connective tissue there are a few regenerated tubules and a few scarred glomeruli, but no remaining mass of necrosed tissue such as is seen in gross R.C N . The most striking appearance however is that the intralobular arteries appear normal; they run a rather sinuous course across the shrunken scarred cortex, with no trace of organised thrombus, intimal proliferation, or alterations in the media.

Macroscopically, in the acute phase of confluent focal R.C.N., the kidney has a red congested cortex, sometimes with punctate haemorrhages and sometimes with a diffuse paler mottling, but it does not show any appearance of white infarcted areas.

CHILDREN

The majority of cases of R.C.N. in children are of confluent focal type. In some cases the renal disturbance follows immediately after a sudden attack of diarrhoea and abdominal pain, and cases in babies may follow an indefinite time after gastro-enteritis. Another group originates at about 7 to 9 days after an attack of tonsillitis. The remaining recorded cases developed a few days after pneumococcal infections or peritonitis.

CASE NOTES

The following 3 cases, all examples of confluent focal R.C.N., have been examined in the present study; (for the first two, we are indebted to Dr. E. G. Hall).

CASE 68. Male, age 4 years. Appendicitis with perforation. Laparotomy. Blood urea normal 5 days later. Then complete anuria for 32 hours to death.

The kidney showed a confluent focal R.C.N., so extensive that the entire cortex was involved. There was thrombosis of some stalk afferent vessels and glomerular capillaries, but no arterial lesions were present. The renal lesions were of uniform development, and were estimated histologically to be of 30 to 36 hours' duration.

CASE 69 Female, age 7 months. Haemolytic anaemia. Diarrhoea and jaundice at 10 days before death Slight haematuria at 3 days before death Anuria for, at any rate, the last 48 hours. The blood urea was 500 mg. per 100 cc. at 24 hours before death

The kidney showed lesions of two distinct age-groups. The inner half of the cortex showed the healed stage of an acute renal lesion. Here the glomerular tufts had old thrombosis, partial necrosis, and frequent adhesions, and there was regeneration of tubules, many of which were dilated. The outer half of the cortex showed a confluent focal R C N, with lesions histologically of various ages from about 1 up to 3 days. There were no arterial lesions. A moderate number of colloid casts were present in the distal convoluted tubules, and the collecting tubules were full of albuminuria casts. The appearances are explicable on the view (a) that a confluent focal R.C.N had occurred in the more mature deeper half of the cortex at some time previously, probably more than 2 weeks before, and (b) that the outer half of the cortex had then become more actively functioning, but had succumbed in the last few days to a recurrence of the confluent focal R.C.N.

CASE 70. Male, age 7 months Vomiting and diarrhoea at 5 to 6 months, with an acute attack 2 days before admission at 6 months. Anuria for 9 days, and blood urea of 300 mg per 100 cc. Then gradual resumption of urine secretion to a daily output of about 300 cc. a day, but the blood urea remained about 300 mg, and he died 34 days after the observed onset of anuria



FIG 64 Healed stage of confluent focal R C N The medulla reaches nearly to the cap[illegible] parts 5 weeks after the onset of the ar[illegible] (Magnification × 4)

The renal cortex showed very different pathological appearances in its outer and its inner parts. The outer three-quarters of the cortex consisted merely of scar tissue (Fig. 64) in which there were scattered tubules which could be either distal convoluted tubules or [illegible]

basophil epithelium, and there [illegible] outer three-quarters of the cort[illegible] focal R C N *The inner quarter* [illegible] severe damage and also of compensatory hypertrophy The lesions in both parts of the cortex were so advanced that no histological assessment of their age could be made

LITERATURE

From the reports in the literature, it is often difficult to form any conclusion as to the duration of the R.C.N.. For this reason the cases are given in date order in each of the subsections.

CONFLUENT FOCAL R.C.N.

Herzog (1913, Case 2) Female, age 10. Peritonitis Duration unknown.
Fahr (1925, Case 1). Male, age 4 Dysentery. Duration unknown.
Blackman and Rake (1932). 9 cases among 95 examples of pneumococcal infections.
Bell (1937, Case 56). Female, age 5 months. Pneumococcal peritonitis.
Campbell and Henderson (1949). Case 1. Female, age 10½. Sudden vomiting and [illegible]

Gastro-enteritis for 1 month Very early renal lesions.
Zuelzer et al. (1951) Case 6. Female, age 6 weeks. Diarrhoea. Duration ? 18 hours. Case 7. Male, age 18 days Diarrhoea. Duration ? 2 days. Case 8. Male, age 6 weeks. Diarrhoea. Duration ? 1 day. Case 9. Male, age 2 days. Little more than tubular necrosis of 12 hours duration [illegible] for 3 weeks At autopsy, tubul[illegible] age 12 years Tubular necrosi[illegible] Glomerular thrombosis of ? 2 days duration. Case 13. Infant, age 7 months. Pneumococcal septicaemia. Glomerular thrombosis of ? 24 hours duration.

PATCHY R.C.N.

Bell (1937, Case 35/730) Male, age 9. Pneumonia followed by anuria. Duration unknown.
Dunn and Montgomery (1941) Case 5. Female, age 8. Sudden diarrhoea. Anuria immediately after, continuing to death 4 days later. Case 8. Male, age 9 Tonsillitis (? scarlatina) Anuria began 7 days later. Died after 6 days anuria.
Åkerrén (1947) Female, age 8½. Tonsillitis. Oliguria began 8 days later. Died after 18 days oliguria.
[illegible]

OBSTETRIC CASES WITHOUT U.P.A.

R.C N. occurs in a small number of patients following criminal abortion, and in these cases it is almost always a confluent focal R.C.N.. There are a few other cases of R.C.N. of more classical type which develop sometimes before delivery and sometimes in the puerperium, but are not associated with U.P.A. or hypertensive toxaemia.

CASE NOTES

Only one example of this condition has been examined in the course of the present study.

CASE 71. Young woman Criminal abortion, with subsequent uterine sepsis. Anuria for an unknown time before death.

The renal cortex was almost completely involved by confluent focal R.C N. Most of the glomeruli showed thrombosis of capillary loops or stalk afferent vessels; others showed gross stasis, and many were fully necrosed. Nearly all the proximal convoluted tubules were necrosed, and epithelial regeneration was beginning, indicating a duration of about 3 to 4 days. The arteries were normal

LITERATURE

This particular series of cases is arranged according to the time after delivery, but this is not necessarily the time of development of the R.C.N., which may have begun before or after the delivery.

CONFLUENT FOCAL R C N.

Tillman (1934, Case 2) Age 21. Hyperemesis Died undelivered Kidney pathology atypical

Immink (1930) Age 36, para 7, gestation 35 weeks Died 15 hours p p. Anuria for 2 days before delivery Section, live baby and no U P.A

Fahr (1934). Age 40. Abortion at 13 weeks Died 3 days p p

Hertig and Mallory (1946). Age 23. Abortion at 15 weeks. Died 5 days p p

Jeddeloh (1932, Case 2). Age 38 Abortion at 11 weeks. Died 6 days p p

Jardine and Kennedy (1913, Case 3) Age 23. Convulsions at 20 weeks Surgical induction Anuria began 5 days p p Died 7 days p p.

Torrens (1911) Age 29 Abortion at 17 weeks. Died 8 days p.p.

Jeddeloh (1932, Case 1) Age 19 Abortion at 17 weeks. Peritonitis. Anuria during last day Died 9 days p p.

Atherton (1946) Age 23 Abortion at 7 weeks. Died 26 days p.p.

MINOR R C N.

Lindeboom and Bouwer (1950). Age 23 Dissecting aneurysm of aorta at 31 weeks gestation. Died undelivered 1½ days later.

PATCHY R C N.

Tomlinson (1945). Age 28, para 3, gestation 38 weeks. No eclampsia or U P.A., Manual removal of placenta Died 6 days p p.

Klotz (1908) Age 25, para 1, gestation 35 weeks. Elective caesarean section for oedema and albuminuria. No evidence of U.P A., Died 13 days p p.

Kellar and Arnott (1933, Case 1) Age 26, para 1, gestation 22 weeks Hyperemesis with anuria Hysterectomy No U.P.A . Died of peritonitis over 17 days p p

Gareiss-Dollitzsturm (1928). Age 36, para 8, gestation unknown Staphylococcal septicaemia 5 days p p, and died 25 days p p R C N. appears about one week old.

ADULTS AND ADOLESCENTS

This group includes adult men, non-pregnant women, and adolescents over 13 years old. It is of interest that the incidence is over twice as great in males as in females. In many of the cases there is a sudden attack of abdominal pain, vomiting and diarrhoea; anuria usually develops immediately afterwards, but it may be delayed a few days. Other cases have lumbar pain at the onset of the clinical symptoms. Sometimes the R.C N. is a sequel to tonsillitis, which may have occurred 7 to 9 days or even longer before the onset of the anuria. A few cases follow upper abdominal *catastrophes such as perforation* of a peptic ulcer, acute pancreatitis, or trauma in that region.

CASE NOTES

Three cases of this type have been personally studied; (for these we are indebted to Dr R. Rawcliffe, Dr. L. Wise and Dr. C. A. St. Hill).

CASE 72. Female, age 26. No pregnancies. Nasal polyps producing much discharge. Developed severe epistaxis and was ill subsequently. Seven days later the nasal polyp was removed under general anaesthesia Subsequently she developed bronchopneumonia, and died suddenly 3 days after the operation. No observations on urine.

To the naked eye, the kidneys were slightly enlarged and showed occasional tiny

necrosed tubules These lesions were judged histologically to be about 10 days old. (b) Most of the remaining nephrons showed quite recent lesions; there was much benign

convoluted

old. There

fluent focal

R C.N. which had developed in two episodes. a slight one about 10 days before death, and a severe one 18 hours before death

The spleen showed a typical *fleckmilz* with innumerable areas of necrosis about the size of peas. Histologically the necrosed arteries here showed the same dilatation and thrombosis which is seen in patchy cortical necrosis of the kidney. These arterial lesions and the infarcted areas of the splenic pulp had an apparent histological age of about 3 days.

CASE 73 Female, age 40. No pregnancies. Vomiting and frontal headache 3 days before death, but no diarrhoea. Anuria for 29 hours before death. Twenty-four hours before death she had an epileptiform attack followed by deep coma Two subsequent fits, and died suddenly.

To the naked eye, the kidneys were enlarged and the cortex showed extensive red streaks and pin-head petechiae. Histologi- lesion was a C.N. of about 30 hours' duration. Most tubules in iate zone with colloid casts Similar casts were seen in a few oluted tubul x.

The descending colon showed gross slight on, suggestive of a haemorrhagic infarction.

CASE 74. Male, age 15. Enteritis due to S Normal for

3 days. Then passed a little bloody urine and had anuria for next 4 days to death. B.P. 140/100; blood N.P.N. 120 mg. per 100 cc.

The kidney showed gross R.C.N of about 3½ days duration, with mural thrombosis and basophil intimitis in most intralobular arteries. It is of interest that at this stage there was no occlusive thrombosis in these arteries.

LITERATURE

In many of these cases the duration of the R.C.N. cannot be assessed from the published accounts. The order in each of the following sub-sections is by date of publication.

CONFLUENT FOCAL R.C.N

Bell (1937, Case 57). Male, age 13 Clinically an acute nephritis. Died after 5 weeks' illness.

Lieu (1938). Male, age 35. Abdominal pain and vomiting Anuria followed immediately Died 6 days later.

Dunn and Montgomery (1941). Case 1. Female, age 32 Abdominal symptoms Died [illegible] Diarrhoea Duration unknown Case 3. Female, [illegible] 7 days [illegible] [illegible]e 54. Stokes-Adams syndrome treated by intracardiac adrenalin Died 3 days later [illegible] [illegible]ge 59 Vomiting and anuria for 6 days Case 3 [illegible] 4 or 5 days before death. Case 4. Male, age 64. [illegible] 3 days.

MINOR R.C.N

Penner and Bernheim (1940) Case 1 Male, age 49 Strangulated hernia and peritonitis. Died 7 days later. Case 2 Male, age 68 Carcinoma rectum. Died 11 days after colostomy

Blainey (1952, Case 1) Male, age 14 Appendicitis Vomiting began 10 days later. Died after 2 days.

PATCHY R.C.N

v. Recklinghausen (1883) Case 1 Male Following transfusion of lamb's blood for bleeding gastric ulcer Complete anuria to death 2 days later Case 2 Died 9 days after gunshot wound of lung.

Friedlander (1883) Female, age 36 Anuria commenced 18 days after scarlatina Died 5 days after onset of anuria

Stoeckenius (1921). Male, age 46 Anuria began 9 days after tonsillitis. Died 7 days after onset of anuria.

Bamforth (1923) Male, age 37. Had dysentery, and died 10 days afterwards. Anuria for last 2 days of life

Zalka (1933) Case 1 Female, age 13 Tonsillitis Anuria began 9 days later. Died after 10 days' anuria, with peritonitis. Case 2. Male, age 64 Coronary thrombosis. Oliguria Died 4 days later.

Ash (1933) Case 1 Male, age 25 Sudden abdominal pain, vomiting and diarrhoea. More or less complete anuria to death at 17 days Case 2 Male, age 32. Sudden abdominal pain and vomiting, followed at once by anuria, which was succeeded by oliguria after first week. Died at 21 days.

Garvin and Wezel (1938). CASE 1. Male, age 40. Died $2\frac{3}{4}$ days following drinking of "almond extract" Centrolobular necrosis of liver. CASE 2. Female, age 53. Died in 6 days, no details Centrolobular necrosis of liver. CASE 3. Male, age 24. Died at $5\frac{1}{2}$ days. No other details. Centrolobular necrosis of liver.

Benson (1938) Male, age 35. Died 12 days after onset of lumbar pain and nausea.

Lanza (1938). Male, age 49 Died on 13th day of malarial therapy for syphilis

Azevedo and Teixeira (1938) Male, age 15. Died on 26th day following snake bite.

Hunt (1939). Male, age 35. Thrombocytopenic purpura for months. Coryza for 4 days, followed by rigor and anuria. Died $8\frac{1}{2}$ days later.

Weaver and Haam (1939). Male, age 17. Tonsillitis 90 days before death. Anuria for 2 days before death. Heart 450 gm.

Tuta and Vander-Kloot (1940) Female, age 50. Died 9 days after onset of abdominal symptoms, and 6 days after onset of anuria.

Dunn and Montgomery (1941) CASE 4. Female, age 67. Carcinoma of right ureter with calculus. Other kidney showed R.C N . Oliguria for 8 days. CASE 6. Male, soldier. Ill a few days. CASE 7. Male, soldier Lumbar pain and anuria for 6 days to death.

Polayes (1941) No clinical details.

McFarlane (1941) Male, age 65 Accident with much trauma, including injuries to liver, spleen and left kidney. Died 36 hours after accident. Right kidney showed an early stage of R.C.N

Brown and Crane (1943). Female, age 32. Severe burns. Great oliguria to death 6 days later.

Brandt (1949). Male, age 69. Died 4 days after drinking 3 litres of brandy.

GROSS R.C.N.

Juhel-Rénoy (1886). Female, age 16. Scarlatina. Anuria began on 8th day. Died on 14th day

Apert and Bach (1928). Male, age $13\frac{1}{2}$ Abdominal pain. Died 7 days later.

French (1940) Male, age 38. Anuria developed one day after onset of acute pancreatitis. Died 10 days after onset of anuria.

Godwin and McCall (1941). Male, age 45. Perforated gastric ulcer. Anuria began at $4\frac{1}{2}$ days Died at 6 days Peritonitis

Juzbašic and Sarre (1941) Male, age 28 Pains in loins, fever and anuria. Biopsy on 3rd day showed that the intralobular arteries were necrosed and some were filled with thrombus. The glomeruli sometimes showed stasis, sometimes were thrombosed, and sometimes completely necrosed. The tubules around were mostly necrosed but still retained pyknotic nuclei. At autopsy, 2 days later, the kidneys showed gross R C.N.

Mallory (1948) Female, age 61. Addison's disease with crisis on day before death.

Miller (1949, Case 1) No clinical details. Biopsy of kidney after 5 days' anuria showed massive necrosis of cortex resembling an infarct.

Werner, Muckerman and Allen (1950). CASE 1. *Female, age 26. Virus pneumonia.* Died 10 days later CASE 2. Female, age 29 *Incompatible blood transfusion 10 days* after normal delivery.

OTHER CASES

A special series of cases of R.C.N. of varying degrees of severity have occurred as a result of dioxan and of diethylene glycol poisoning: Barber (1934) 5 cases; Hagebusch (1937) 4 cases; Ruprecht and Nelson (1937) 5 cases; Brindley and Kelsey (1938) 1 case; Geiling and Cannon (1938) 8 cases. The

lesions in these kidneys are the same as those in any spontaneous R.C.N., and are collected here only because of their distinctive aetiology.

Four cases commonly quoted as R.C.N cannot be accepted as unequivocal examples of this condition. In the case described by Matthias and Pincsohn (1925) the patient had heart disease and possibly a ruptured aneurysm of the renal artery The naked-eye description of the kidney does not agree satisfactorily with the microscopic appearances. Iungano (1927) recorded a case of embolism of the left renal artery and, 6 weeks later, of the right renal artery; the kidney appears to have been completely necrosed Furtwaengler (1927) described a patient aged 22 who had traumatic rupture of the liver and died 60 hours later. The macroscopic appearances were not those of R C N and the histological lesions may have been due to autolysis In the case recorded by Weber (1909) as early R.C N in a man, the description of tubular necrosis is quite typical of post-mortem autolysis, even to the presence of clumps of bacteria of post-mortem growth.

A few cases recorded as R.C N. have not been available for analysis in the present review (Zanzig, 1915; Tecoz, 1942; Cocuzza and Silva, 1947, Sanhueza and Valenzuela, 1948; Amoroso, 1949; Migone and Tardini, 1951; Lucia, 1951).

CHAPTER XI

DISCUSSION OF GENERAL PATHOLOGY

The course of development of the various pathological lesions will be discussed in two main parts. The present Chapter deals with the basic circulatory disturbance which is responsible for all the lesions, and with the general pathology of the effects of this disturbance. The next Chapter is concerned with the special pathology of each of the lesions in turn.

AETIOLOGY OF THE RENAL LESIONS

There can be no doubt, from the pathological appearances, that the tissue death of R.C.N. is ischaemic in origin; it is clearly a particular type of infarction.

The evidence with regard to the aetiology of the less severe lesions is however somewhat indirect.

(*a*) The renal lesions which follow U.P.A. form a graded series exemplified by the following conditions in order of decreasing severity: R.C.N. [illegible] convoluted tu[illegible] albuminuria. T[illegible] and the severe degrees of proximal convoluted tubule necrosis. In a series of kidneys which are involved mainly by extensive proximal convoluted tubule necrosis, one may show no glomerular thrombi; another may show numerous benign glomerular thrombi; another may show, in addition, small areas of focal R.C.N. Conversely, whenever a kidney shows R.C.N. in one part of the cortex, the remaining parts of the cortex always show extensive tubular lesions.

It is reasonable to postulate therefore that all the lesions are due to one common local aetiological factor, operating with different degrees of severity.

(*b*) The distribution pattern of the lesions in the cortex shows broad similarities in R.C.N., in proximal convoluted tubule necrosis, and in colloid degeneration. The distribution can not be identified in the case of uncomplicated albuminuria, but there is no evidence that it has a different pattern from that of the other lesions. This general similarity of the pattern suggests a common aetiology related to the vascular architecture.

(*c*) All the lesions can be produced experimentally by subjecting the kidney to ischaemia. These experimental lesions form a severity-series corresponding closely to the series observed in human kidneys, and the severity of the experimental lesions depends on the duration of the ischaemia. The shortest ischaemia produces only an albuminuria, the longest produces cortical necrosis. This subject will be discussed in another paper.

(*d*) It must be admitted that the necrosis of the proximal convoluted tubules shows some similarity to that produced by chemical tubular nephrotoxins. However, in the present cases the tubular necrosis can be satisfactorily explained as a result of ischaemia alone (c.f the tubular necrosis at the margin of any embolic infarct). It is impossible to disprove that a tubular nephrotoxin may also be present, but the postulation of any such synergistic factor appears unnecessary.

The explanation that all the lesions, from R.C.N down to simple albuminuria, are due to varying degrees of ischaemia will be accepted for the above reasons. There is a further line of evidence sometimes adduced to prove the existence of ischaemia (Larson and Bennett, 1939; Solymoss, 1949, De and Sengupta, 1951) which is however not valid. This consists of the demonstration of the distribution of blood in the kidney after death, with the inference that this represents the circulatory state in the kidney during life. It is necessary to emphasise that, in histological sections of normal or pathological kidneys, the absence of blood from vessels which are not necrosed or obstructed is no indication whatsoever as to the bloodflow in them during life In the normal kidney the renal bloodflow is about 3 to 5 cc. per gram per minute, and, by suitable stimuli, it can be varied in the range of 0 2 cc. up to 10 or 12 cc per gram per minute (Herrick, Mann and Sheehan, 1939) There is much blood throughout the entire vascular system of the kidney during life, and the cortex has a red colour After the death of the patient, the intra-capillary pressure disappears Within a very short time the agonal contraction of arteries and capillaries, and other factors such as tissue tension, lead to a redistribution of blood in the kidney, so that the cortex becomes pale In the process of cutting and fixing the kidney, some of the blood remaining in the cortex is likely to escape As a result, the normal kidney when examined histologically has little or no blood in the cortical arteries or capillaries, and practically none in the glomeruli; on the other hand, the vessels in the intermediate zone and to a less extent in the medulla usually contain blood This is clearly not the pattern of the blood distribution during life. Histological study is not on this account entirely valueless. In the pathological kidney, reliable deductions as to the bloodflow during life can be drawn, and in fact are drawn here, from the histological finding of acute ischaemic lesions of parenchyma or vessels, or from the finding of stasis or thrombosis in vessels

The histological appearances of arteries and capillaries in post-mortem tissues can give some indication of their functional condition before the death

the sudden fall in blood pressure at death, the muscle cells in the walls contract so that the lumen is considerably reduced Subsequently this agonal spasm

relaxes, and the arteries take up a cadaveric position with the internal elastic lamina showing its normal wavy appearance

The significance of the agonal contraction of arteries and capillaries is well illustrated in the specific example of recirculation of blood through the glomeruli of the centre dead area a few weeks after the R.C.N. has occurred. The capillary loops of these [illegible], a result, the blood which was [illegible] in them after death, giving the [illegible]o.

There are three main conditions in which the agonal contraction fails to occur:

(*a*) In a tissue where there has been an acute inflammatory reaction of some standing. Here the capillaries remain in a fixed dilatation after death, and a lesser degree of this phenomenon is seen in small arteries. It appears that the muscle cells in the walls are paralysed, possibly as a result of prolonged dilatation or of toxins.

(*b*) In local lesions of arterial walls, either acute as in periarteritis nodosa or chronic as in atheroma, there is frequently a loss of contractility of the arterial wall at this site, so that the internal elastic lamina is seen as a straight line in sections.

(*c*) Where an artery has been in spasm for some time before the death of the patient, this spasm can lead either to a paralysis or to death of the muscle cells. The occurrence of paralysis without death of the arterial wall can be identified in small arteries of the kidney in a variety of pathological conditions. The arterial wall is stretched but not disrupted and shows no necrosis of its walls, though there may be some degenerative changes in the media. It is of interest that in such cases there is usually no necrosis of renal parenchyma, though there may be lesser grades of ischaemic damage. The probable explanation is that there has been a very intermittent spasm of the artery for several hours, though it must be conceded that toxins or other factors might play a part.

What is of much more significance in the present connection is the occurrence of dilatation of arteries in R.C.N.. In the cases which are interpreted as early R.C.N the arteries usually show acute lesions, such as blood cells in their walls, similar to those which are seen in fully developed cases of R.C.N.. In the late cases of R C.N the arterial wall undergoes necrosis which proceeds *pari passu* with the necrosis-changes in the surrounding tissue. It appears therefore that the absence of agonal contraction in the early cases of R.C N. is indicative, not merely of paralysis, but of death of the media.

CAUSE OF THE ISCHAEMIA

As will be explained later in the discussion, the course of development of all the different types of lesions during the first 12 hours gives clear evidence of the following sequence:

(*a*) There is an initial period of total or almost total ischaemia. This period is of variable duration, lasting in some cases only a few minutes and in others for as long as 6 or 7 hours. If it is of short duration, it damages the renal parenchyma; if it is prolonged, it kills the tissue.

(*b*) Subsequently the ischaemia passes off, sometimes permanently but sometimes only temporarily. Following the period of ischaemia, there is a reflow of blood through the area This occurs in all types of lesions, from mere disturbances of glomerular filtration right up to R.C.N.

The proof of this sequence is too extensive to be given at this particular point in the discussion, but the concept is essential to the understanding of the whole pathology. The various complications of this basic sequence need not be considered at the present juncture.

This occurrence of ischaemia followed by a reflow of blood can only be satisfactorily explained by the occurrence of a spasm in the cortical arterial tree, followed by a relaxation of the spasm. Differences in the duration and the distribution of this spasm account fully for all the differences between the resulting lesions

A great variety of other explanations have been given in the literature. These require consideration.

Thrombosis The ischaemia which gives rise to all the less severe lesions, up to and including proximal convoluted tubule necrosis, is never associated with thrombosis of cortical vessels, either during the first 12 hours or subsequently, and thus cannot be ascribed to thrombosis

In cases of R.C.N., although thrombosis is always found later, it is never present before 14 hours At this time extensive tissue necrosis has already occurred. This necrosis can thus not be a result of thrombosis.

Glomerular stasis. It has been suggested that the primary lesion in R.C.N. is a dilatation of glomerular capillaries with stasis in them (Cortese, 1935; Dunn and Montgomery, 1941, McFarlane, 1941; Heggie, 1949; Blainey, 1952) The [illegible] developed

Swelling of tubular epithelium Another theory is that, in the early stage of R C N , the tubular epithelium becomes greatly swollen and compresses the intertubular capillaries, thus producing a mechanical arrest of the circulation This explanation is not acceptable for two reasons. Firstly, in the early stages of R.C.N or of proximal convoluted tubule necrosis, the kidney is of normal size and weight, and histological sections, using any technique, do not show any swelling of the epithelium. Secondly, there are two conditions where an acute and very great swelling of renal tubular epithelium does in fact occur,

sufficient to produce a significant increase in the weight of the kidney: viz. in patients treated with large amounts of intravenous hypertonic glucose solution, and in rabbits after administration of dioxan or diethylene glycol. In neither of these conditions does R.C.N. result.

Intertubular oedema A variant on the previous hypothesis is that intertubular oedema is responsible for the arrest of the bloodflow. In fact, intertubular oedema does not become recognisable, either histologically or by the increased width of the cortex and increased weight of the kidney, until about 2 or 3 days after the renal lesions have developed. In extension of this view, it is sometimes maintained that, even in this late stage, the renal circulation is impaired by the intertubular oedema, so that the lesions in the kidney progress. Against this, it may be pointed out that there is no evidence of any extension of the necrosis after the oedema develops; on the contrary, there is active repair of tubules in the oedematous cortex from that time onwards.

Lowering of general blood pressure. Several authors have postulated that R.C.N. is caused by a reduction of renal bloodflow as a result of a fall of the general blood pressure which occurs during the shock. In fact, as has been shown in Chapter II, the blood pressure is usually well maintained during the phase of shock in these patients. A variant of the hypothesis is that, though the blood pressure is not low by absolute measurements, it is low relative to what it may have been before the U.P.A. occurred. The proponents of this theory do not make it clear how this relative lowering would account for R.C.N.. However, the basic objection to this general explanation is that R.C.N. is not a complication of retained placenta, post-partum haemorrhage, or other obstetric conditions which lead to severe shock or great loss of blood

RESULTS OF THE ISCHAEMIA

This subject will be considered under two headings: first, the damage to or death of the tissues as a result of the interruption of their blood supply; second, the subsequent alterations in these dead or damaged tissues.

THE DIRECT EFFECT OF THE ISCHAEMIA

The severity of the damage to the kidney is related to two variable factors: the duration of the ischaemia, and the sensitivity of the different structures to ischaemia.

A very short period of ischaemia produces no obvious effects; a somewhat longer period damages but does not kill the most sensitive structures; a longer period kills these sensitive structures and produces non-lethal damage to the more resistant structures; a very long period kills all the tissues.

The gradient of sensitivity of the different structures in the renal cortex to ischaemia can be assessed from two sources of evidence: (*a*) The identification

of the earliest time after the U.P.A. at which each structure shows recognisable necrosis. This time represents the period of ischaemia required to produce death of the structure plus the subsequent period required to allow recognisable necrosis-changes to develop The duration of this second period can be assessed approximately, from considerations discussed in the next section. Thus an estimate can be made of the actual time of ischaemia required to kill each type of tissue. Non-lethal damage to these structures presumably requires a lesser duration of ischaemia. (*b*) The other line of evidence is obtained from experimental observations. These, though more accurate in themselves, have to be interpreted from animal to human pathology

The estimates of duration of ischaemia given for each of the lesions in the present study are only approximate; they are given here more as indications of their proportions to one another than as absolute periods of time. In particular, the periods given in sections *c* to *g* may be over-estimates.

Details of sensitivity The different structures in the renal cortex appear to have the following gradient of sensitivity to ischaemia:

(*a*) Most sensitive is the integrity of the glomerular filtration mechanism, with particular reference to its impermeability to plasma proteins During the actual period of the ischaemia there is no evidence of damage to this filtration mechanism, because there is a complete absence of filtration. It is only when the circulation is re-opened subsequently that gross proteinuria occurs. The duration of ischaemia which is necessary to produce damage to the filter is in the region of quarter to half an hour

(*b*) The epithelium of the proximal convoluted tubules The most sensitive part is the neck near the glomerulus; the remainder of this tubule, including its spiral segment, shows a diminishing sensitivity in relation to the distance from the glomerulus. Even in a single short segment of the tubule, where all the epithelium presumably suffers the same degree of ischaemia, most of the cells may die while occasional cells, either isolated or in small groups, may survive There are also differences of sensitivity between one nephron and its neighbour, presumably dependent on differences in their functional activity at the time when the ischaemia begins. Thus one proximal convoluted tubule may be killed while the next one, lying beside the same capillary, is almost undamaged These differences in sensitivity are however of little importance as compared with the differences in the amount of ischaemia suffered by the tubules in neighbouring areas of cortex.

The duration [illegible]

to these tubul

and colloid d

rather more for the latter Death of these tubules probably results from about 2 to 3 hours of complete ischaemia This latter figure is important, because it is fairly well established, and because it forms a definite point of reference for the

time-relationships of the less severe and the more severe lesions. The precise time required to produce death of the proximal convoluted tubules in the human kidney is not known, but it may be assumed to be of somewhat the same order of magnitude as in other mammalia. In rats (Koletsky and Gustafson, 1947) and in rabbits (Scarff and Keele, 1943) a complete ischaemia lasting about 2 hours kills most of these tubules. In dogs the tubules are less sensitive, and some of them may survive an ischaemia of nearly 4 hours (van Slyke et al., 1944). In the present discussion, an intermediate figure of 3 hours is arbitrarily adopted for the human kidney.

(*c*) The endothelium of the capillary loops and stalk afferent vessels of the glomeruli, and the contractility of these structures. This endothelium seems to suffer severe damage after a longer ischaemia, perhaps somewhere in the region of 5 or 6 hours, though there are variations similar to those described in the case of proximal convoluted tubules.

(*d*) The epithelium of the distal convoluted tubules and of their continuation into [illegible] ex. The collecting tubule [illegible] tubule. The duration of ischaemia required to kill these structures may be assessed at somewhat longer than 6 hours. Whenever these structures are killed, the area seems always to be in an early stage of R.C.N.

(*e*) The endothelium of the intertubular capillaries.

(*f*) [illegible] It is rather

[illegible]

insensitivity is particularly striking in view of the close relationship of the epithelium of the glomerulus to the epithelium of the neck of the proximal convoluted tubule An ischaemia lasting perhaps about 6 or 8 hours is necessary to kill these cells

(*g*) The walls of the arteries, including in particular the intima and the media. Their sensitivity can be assessed from the time of development of recognisable arterial lesions in minor R.C.N.. In general it may be estimated that the arteries can withstand a period of about 8 to 12 hours' ischaemia before they die, though their contractility is probably lost earlier.

SUBSEQUENT CHANGES IN THE DAMAGED OR DEAD PARENCHYMA

As has already been mentioned, if the ischaemia is of only short duration the tissues are damaged but not killed. Histologically they appear normal at the end of the period of ischaemia, as is well known from experimental work. However, when the ischaemia passes off and the bloodflow is re-established, these damaged cells undergo various changes which may be accepted as the reactions of live cytoplasm. Within a few hours hyaline droplet formation and colloid degeneration appear in some of the proximal convoluted tubules.

When the tissues have been deprived of a blood supply for more than a certain time, they are killed. During the continuance of the ischaemia, the dead tissues show remarkably little histological change for several hours (Wieszeniewski, 1912). In experimental animals, the damaged and the dead cells can be demonstrated at this time by their reaction to vital stains, but not by ordinary fixation and staining. This latter method is the only one applicable to human tissue at autopsy

It is a truism that the histological identification of the process which is described as "necrosis" consists of the recognition, not of the actual death of the cell, but of the necrosis-changes which develop subsequently in the dead cell What is less well known is that the rate of such necrosis-changes in dead [illegible]

paper, but the influence of the same factor can be observed equally well in the present pathological material

The course of the necrosis-changes varies in certain particulars from one tissue to another It can be studied most easily in the proximal convoluted tubules, because there are many circumstances in which these tubules are killed by ischaemia; in certain of these conditions there is subsequently a good bloodflow around them, while in other conditions they receive little or no further bloodflow.

Proximal convoluted tubules In an ordinary case of proximal convoluted tubule necrosis, the initial period of ischaemia lasts about 3 hours, and the reflow of blood then begins After about 3 hours of reflow the dead tubular epithelium shows recognisable early necrosis-changes, such as pyknosis of the nuclei and alterations of the structure and staining properties of the cytoplasm. These necrosis-changes progress fairly steadily in the presence of a continuing bloodflow, so that, after 12 hours' reflow, the nuclei are almost completely lysed and the dead epithelium shows sleeve-separation with radial fracturing. With experience, it is not difficult to make a reasonably accurate histological assessment of how long the reflow must have continued to produce that degree of development of the necrosis-changes which is observed in any particular case. This duration, plus the 3 hours allowed for the initial ischaemia, always agrees closely with the time which has elapsed from the onset of the U P A. to the death of the patient

At the other end of the scale there are kidneys in which the other evidence indicates that, for all practical purposes, there has been no reflow of blood past the dead proximal convoluted tubules. This is seen in some of the tubules in the centre dead area of gross R C N. These tubules appear practically normal for several hours after the onset of the ischaemia The nuclei become pyknotic very

slowly, and remain stainable for over 7 days and sometimes for 10 or 12 days. The cytoplasm undergoes little change in the early stages but, *during the next* few days, it gradually becomes less solid in appearance and less *eosinophil*

Between these two extremes, there are a variety of other *appearances of* dead proximal convoluted tubules, where the *necrosis-changes have developed* only partially because of the inadequacy or the short duration of the reflow. This is best exemplified by certain of the proximal convoluted tubules in the centre dead area of gross R.C.N.; the necrosis-changes in these tubules have a different course from those mentioned in the last paragraph In this special case, there is the initial period of ischaemia which leads to death of these tubules, and subsequently there is a short period of recirculation of blood, which allows the usual necrosis-changes to begin in them. This reflow ceases after a short time, and the necrosis-changes in the tubules are thus arrested Subsequently these tubules remain relatively unchanged in appearance, though they gradually undergo the very slow necrosis-changes which are characteristic of completely ischaemic tissue.

Glomeruli The necrosis-changes in dead glomeruli are slower than those in dead proximal convoluted tubules, but appear to depend on the recirculation of blood in much the same way.

Thus, in a small focus of R.C N. where a collateral capillary circulation is quickly established, the nuclei soon become pyknotic, and disappear within a day or two. On the other hand, in the large centre dead area of gross R.C.N., there is only a poor and patchy recirculation of blood after the initial ischaemia, and this recirculation is very soon arrested. In such an area the glomerular nuclei become pyknotic very slowly, and remain recognisable for a week or ten days.

Distal convoluted tubules. The dead distal convoluted tubules show a different course of necrosis-changes from those in the proximal convoluted tubules. It is impossible to say how they would respond to a satisfactory recirculation of blood around them; when the ischaemia has lasted long enough to produce death of these tubules, there is practically never any significant reflow of blood through the area. However it is a striking fact that, in an area which appears to have an almost uninterrupted ischaemia, these dead tubules can undergo the dissociation into individual cells and the nuclear distortion which have been described in Chapter V. The nuclei of these tubules disappear finally after about a week to 10 days, as in the case of the other nuclei of the area.

Intertubular capillaries. The endothelium of intertubular capillaries is killed only in areas where the ischaemia is prolonged and R.C.N. is developing. In these areas there is only a poor and transient reflow of blood before the final and permanent ischaemia occurs. *This short reflow is insufficient to produce* much change in the endothelial nuclei. During the continuous ischaemia

which follows, these nuclei slowly become pyknotic, and disappear in the course of about 7 to 10 days.

Arteries. The changes in dead arteries form a particular case. Thrombosis occurs very quickly after the blood re-enters these dead vessels, and there is thus a permanent arrest of the circulation very soon after the attempt at its re-establishment. There are various effects during the short period when blood flows back under pressure into the lumen of the dead artery, and these produce a special series of changes which are discussed in detail in Chapter XII.

Dehaemoglobinisation. One of the clearest indications of the absence of recirculation of blood in an area is the development of dehaemoglobinisation of the red corpuscles which have been trapped there This subject has been discussed in detail previously and will not be further considered here, apart from mentioning two facts: (*a*) Dehaemoglobinised red corpuscles indicate that there was a bloodflow in the area 24 hours before, but that it ceased over 12 hours before (*b*) The absence of any red corpuscles in the area (as a result of their disintegration) indicates that no blood has flowed through the area during the past 24 hours.

Marginal zones The necrosis-changes at the edge of a large area of R C N. provide a special example. Here a partial blood supply is obtained through capillary anastomoses from the surrounding tissue. In this instance, the rate of the necrosis-changes in the dead cells depends on their proximity to tissue where there is freely circulating blood. Thus at the periphery of the area the necrosis-changes occur rapidly, further in they occur more slowly, and at the centre, where there is complete ischaemia, they progress extremely slowly The picture is of course further complicated, because the duration of the initial ischaemia has also varied

VASCULAR SPASM

In an early section of this discussion, it was pointed out that the ischaemia varied in duration in different cases, and that it was followed by a temporary or permanent recirculation of blood through the area The general conclusion was reached that this particular course could only be explained satisfactorily by severe spasm in some part of the arterial tree. The details of this spasm will be considered in the present section

NATURE OF THE SPASM

In this paper, the phrase "operative spasm" is used to indicate a spasm which results in observable ischaemic lesions This effect implies that there must have been total or almost total closure of the lumen of the vessel for some minimum period of time. It is possible that the less severe lesions may be the result of incomplete or intermittent spasm For convenience, the duration of the spasm,

whether complete or incomplete, is expressed in terms of the duration of total and uninterrupted ischaemia which is known to produce the same lesions. For example, the proximal convoluted tubules might conceivably be killed by an ischaemia lasting 5 hours but remitting for 10 minutes at the end of each hour; this would be considered here as representing 3 hours of complete ischaemia. The occurrence of intermittence of the ischaemia will be discussed later.

When either the whole or part of a vessel is in operative spasm, the significant site is the point where the bloodflow is arrested and, beyond which, the ischaemic lesions develop The question of whether the spasm only affects a short segment of the artery, or whether it also involves all the distal arterial tree as well, is of purely academic interest in the present connection.

Site of the operative spasm. The position of the operative spasm can be identified, in sufficiently advanced cases of R.C.N., by the site of the proximal end of the necrosis of the arterial walls and of the related thrombosis. In the early cases of R.C N. and in the less severe conditions, neither of which are accompanied by recognisable vascular lesions, the site of the operative spasm can be inferred from the distribution of the parenchymal lesions.

In a fully developed case of gross R.C N., the proximal end of the arterial damage is usually at about 0.5 to 1 mm. from the origin of the intralobular artery; this spares the blood supply to the juxtamedullary nephrons and to the medulla. In cases of patchy and of minor R.C.N., the vascular lesions occur further out along the intralobular artery, and the site of the operative spasm must therefore be placed at this more distal position. In cases of focal R.C N. and of benign glomerular thrombosis, the vascular lesions occur only in the afferent arteriole or in the stalk afferent vessel, and the site of the operative spasm must be located there In the less severe glomerular lesions, the damage involves only the capillary loops, and the site of the operative spasm appears therefore to be at the origin of the glomerular capillaries from their stalk afferent vessel.

In the consideration of the lesions which are unassociated with vascular damage, the outstanding fact is that the tubular damage is nephronic in distribution. This can only be interpreted as due to operative spasm at glomerular level, though whether this occurs in the arteriole or at the base of the glomerular capillaries can not be decided. The thesis that the operative spasm is at glomerular level receives support from those slightly more severe cases where proximal convoluted tubule necrosis is accompanied by benign glomerular thrombosis.

In these conditions which are related to operative spasm at glomerular level, there is a clear tendency for certain segments of the cortex to be involved much more than others. This is indicative of an operative spasm involving many or all of the terminations of a particular intralobular arterial tree, while sparing a neighbouring arterial tree. This involvement of all the terminations

of one artery suggests a hypothesis which, though attractive, is not essential to the main argument:—that there may have been an initiating focus of irritation or partial contraction in the main trunk of the intralobular artery, and that this contraction passes along, owing to the structural continuity of the musculature of the arterial tree, to become an operative spasm in the terminal branches at glomerular level. Such a development of operative spasm might occur only in certain glomeruli and not in others; this would account for the less extensive lesions which involve only a few scattered nephrons.

This hypothesis explains some of the basic similarities in the distribution pattern of all types of renal damage, ranging from tubular degenerations up to gross R.C.N.. The most striking feature of this pattern is the immunity from damage of the juxtamedullary nephrons, the occasional subcapsular nephrons, and the radiating bands through the cortex In the cases of gross R.C.N., it has been explained that the operative spasm occurs sufficiently far out in the intralobular artery to spare the origins of the arterioles to the juxtamedullary nephrons. In the cases of purely tubular lesions, the hypothetical focus of irritative contraction presumably occurs at about the same site in the intralobular artery, and passes out to become an operative spasm only in the terminations of the distal arterial tree; in this way, the terminations of the arterioles to the juxtamedullary nephrons would escape involvement in these milder lesions. The reason for the survival of some subcapsular nephrons and of the radiating bands of live tissue will be discussed in the section on the distribution of the lesions in gross R.C N.

THE COURSE OF THE SPASM

When an *early* example of gross R.C N is studied, it is seen that there is widespread necrosis of parenchyma without any vascular lesions at all. Furthermore, there is clear evidence that some patchy reflow of blood has occurred, and that it has been of nephronic distribution; some tubules have

[illegible]

stage corresponding to a 6 or 9 hour lesion, indicating that arterial bloodflow can continue up to this time

The study of rather *more advanced* cases of gross R.C.N. shows that at about 6 to 12 hours there is a sudden cessation of the progress of the necrosis-changes in the dead tubules. This is explicable only by a renewed arrest of the blood-flow. The site of this arrest appears to be near the base of the intralobular artery, though, as there is no bloodflow, no histological evidence of damage develops in the artery at this particular stage.

After this second ischaemia has lasted for 12 to 24 hours, the arterial spasm

passes off and a second reflow of blood begins. This is evidenced by its effects on that part of the artery which has been killed during the second ischaemia: all the parts of the artery distal to the site of the operative spasm become dilated; they show other rapid changes in their walls such as disruption of the media; thrombosis occurs in the lumen. It is at this stage that the site of the spasm which caused the second ischaemia, the operative spasm in the artery, is revealed

This second reflow of blood is never of sufficient duration to allow any significant development of necrosis-changes in the area. Within a short time it is arrested by the occurrence of the thrombosis in the dead arteries or by stasis in the dead glomeruli. From this time onwards there is a permanent ischaemia.

Several days later, the centre dead area of the R.C N. shows: (*a*) The histological picture of necrosis of proximal convoluted tubules which, during the first reflow, has reached various stages of development and then, at the onset of the arterial spasm, has become "fixed". The necrosis-changes have been arrested because they could not proceed during the second ischaemia, nor during the very short second reflow, nor during the final permanent ischaemia (*b*) The thrombosis of arteries which developed during the second reflow.

Though there are two distinct operative spasms, an early one at glomerular level and, after an interval, a later one at arterial level, it must not be supposed that these are unrelated. It may reasonably be surmised either that the glomerular spasm transfers back to the main trunk of the artery to become operative there, or that the initiating focus of partial contraction, which has been postulated in the main trunk, continues there for some period and then suddenly becomes an operative spasm at that site.

TIMING OF THE VASCULAR DISTURBANCE

The duration of the various stages can only be estimated approximately. The degree to which the tubular necrosis-changes have developed can be assessed by reference to the time-stages of the lesions in cases of simple proximal convoluted tubule necrosis This gives an indication of the duration of the initial ischaemia and of the first reflow, though it must be admitted that an unsatisfactory reflow would produce only the same changes as a good reflow of shorter duration. The duration of the second ischaemia, due to the arrest of bloodflow through the arteries, can be gauged from the type of thrombosis; as will be shown later, the different types of thrombosis indicate different durations of arterial ischaemia The duration of the second reflow is probably very short in cases of prolonged arterial spasm, though rather longer in the case of the short spasm which occurs in small arteries; its usual duration is probably much less than 2 hours. In this way, it is possible to make a rough allocation of times to the different stages of the vascular disturbance in any case of R.C.N..

These times can however only be checked in the cases of R.C.N. where death occurs within 2 days after the U.P A.; in these early cases the remaining time-component in the calculations, the duration of the final permanent ischaemia, can be assessed from the degree of dehaemoglobinisation of the red corpuscles. In such cases, the sum of the periods allocated on histological grounds to each stage of the vascular disturbance agrees reasonably closely with the duration of life after the U.P.A.

OTHER GROUPS

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the arterial spasm occurs in the distal segments of the intralobular arteries, and there is little or no evidence of any reflow of blood between the times of the glomerular and the arterial spasms. The probable explanation is that the transfer of the spasm from the glomeruli to the arteries occurs quite early. This arterial spasm affects only small arteries, and passes off within about 14 hours after the U.P A , so that the thrombosis of arteries is seen much earlier in these cases than in gross R.C N.

In focal R C.N. the spasm remains at the arteriole or stalk afferent vessel, and does not migrate back along the artery It continues long enough to produce death of the glomerulus. When the bloodflow is re-established, there is thrombosis or stasis in the glomerular tuft, but no arterial lesions occur.

In purely tubular lesions the initial ischaemia does not last sufficiently long to damage the glomerulus seriously. When the initial glomerular spasm passes off, the bloodflow is satisfactorily re-established in nearly all cases, though during the next few hours an intermittent spasm may recur at the glomerulus, as will be discussed later. The operative spasm is never transferred back from the glomerulus into the arterial tree in cases with these purely tubular lesions.

DURATION OF THE ARTERIAL SPASM

It is of interest that, in the entire series of cases, the facts indicate that the operative spasm at glomerular level is of relatively short duration, whereas that in arteries is always more prolonged. There is evidence, from certain cases of gross R C.N , that the spasm in the larger intralobular arteries can continue for a day or even more This raises the question of how an artery can maintain an operative spasm for so long It might reasonably be expected that the artery would strangle itself at this site, and thus that it would dilate It is possible that just sufficient blood enters the artery at the proximal end of the site of operative spasm to keep that portion of the artery alive and capable of continued contraction. An alternative hypothesis is that, when the portion of the artery at the site of the operative spasm is dying, the spasm is taken up by a short section of

the artery proximal to it. The problem can not be considered as in any way settled. Nevertheless there is no doubt that arteries in general can go into so severe and prolonged a spasm as to produce death of the tissue beyond. This is seen in some cases of Raynaud's disease, ergot poisoning and frostbite. It is also well known that bullet wounds in the vicinity of limb arteries can cause very prolonged segmental spasm of these vessels.

CONCLUSIONS ON VASCULAR SPASM

In this discussion, the development of R.C.N. has been explained on a fairly simple sequence of initial glomerular spasm, first reflow, later arterial spasm, second reflow, and final permanent arrest of the circulation. The less severe lesions require only the first two steps of the sequence. It is freely admitted that the vascular disturbance is almost certainly more complicated. The possibility of intermittence of spasm, variability in the amount of reflow, and the effect of recurrence of ischaemia on structures which have suffered partial ischaemic damage a few hours earlier, are some of the incalculable factors. Nevertheless the general scheme of two ischaemia-reflow sequences seems to be established by the present evidence, and the other complicating factors can only produce variations inside this basic pattern.

The explanation that R.C.N is due to vascular spasm is not in any way new; it was suggested by Friedlander (1883) and Beneke (1894), and has been accepted by many subsequent authors. Various modifications of this explanation have been put forward in the literature, and these have been well discussed in previous reviews (Ash, 1933; Duff and More, 1941; Dunn and Montgomery, 1941; Campbell and Henderson, 1949) Some of these modifications are based on the Ricker theory: that there is a primary vasoconstriction followed by a vasoparalysis, and that this vasoparalysis interferes with the bloodflow so that stasis occurs and R.C N. results (Scriver and Oertel, 1930). This and similar hypotheses do not however account satisfactorily for the occurrence of the series of lesions of less severity than R.C.N.. The significance of these less severe lesions does not seem to have been recognised previously, and thus the theories about the manner of arrest of the circulation have usually been devised only to explain the appearances of fully developed R.C.N.

AETIOLOGY OF THE SPASM

In the literature, it has sometimes been suggested that the spasm is produced by toxins. The toxin postulated is sometimes the "eclamptic toxin" and sometimes the products of the retroplacental haemorrhage, but there is no direct evidence for the existence of either of them. However there is no doubt that various demonstrable toxins can produce R.C.N, presumably by way of arterial spasm. Symeonidis (1949) produced focal or minor R.C.N. in pregnant rats by the injection of progesterone in the last third of gestation. There were

associated liver lesions remarkably similar to those of human eclampsia. Among other toxins may be mentioned dioxan or diethylene glycol in human beings, staphylococcal and other bacterial toxins in experimental animals (Neisser and Levaditi, 1901; Forssman, 1932; Apitz, 1934; Rigdon, Joyner and Ricketts, 1934; von Glahn and Weld, 1935; Gerber, 1936; Glynn, 1937; Navasquez, 1938; Black-Schaffer, Hiebert and Kerby, 1947; Heggie, 1949; Smith and Muirhead, 1951; Thomas and Good, 1951; and several other workers), swine fever virus (Rohrer, 1932), streptococci with serum (More and Kobernick, 1951), and lithium carmine (Reyna, 1936).

On the other hand it is well known that the cortical arteries of the kidney are peculiarly sensitive to a wide variety of neurogenic stimuli (Trueta et al., 1947; Sophian, 1949; Franklin, 1949 and 1950; Daniel, Peabody and Prichard, 1952). It is certainly possible that the particular stimulus of U.P.A. might be followed by a neurogenic spasm in these arteries. There have been several [illegible]

1927; McFarlane, 1941; Lynch and Large, 1951).

The possibility that other factors may also play a part is raised by the experimental production of renal damage by choline deficiency (Griffith and Wade, 1939; Christensen, 1942; Dessau and Oleson, 1947; Baxter, 1948), and by the cases of R.C.N. in non-pregnant patients following throat infections, gastro-enteritis, etc.

It must be admitted that the aetiology of the spasm of the cortical arteries in patients with U.P.A. has not yet been clearly elucidated. There is as yet no certainty even that the renal condition is the result of the uterine disturbance, it is conceivable that both conditions may result from one unknown common factor.

CHAPTER XII

DISCUSSION OF INDIVIDUAL LESIONS

PROTEINURIA

From the evidence in the preceding Chapter, it is accepted here that the proteinuria is a result of damage to the filtration mechanism of the glomeruli during the period of temporary ischaemia, so that the large-moleculed plasma proteins are able to pass through in the glomerular filtrate during the next few days. In the most severe cases, practically pure plasma escapes down the tubule.

It is sometimes suggested that the proteinuria in U.P.A. is due to the presence in the plasma of *some abnormal protein which is excreted by* undamaged glomeruli The existence of such a protein is at present unproved

ALBUMINURIA CASTS

The formation of these casts is dependent on several factors Firstly, it is necessary for protein to be passing down the tubule, probably mainly from the glomeruli after the circulation has been re-established, but possibly with some addition from damaged tubules Every case of U.P.A. has proteinuria and is thus a potential case of cast formation Secondly, for precipitation of the protein to occur in the distal convoluted or collecting tubules, there must be some degree of concentration of the filtrate and alteration of its pH (Baker and Dodds, 1925); this requires that there should be continuing tubular function As would therefore be expected, *the casts are formed only in live tubules, they* are never seen in an area of R.C.N.. In addition, the flow of urine down this part of the tubule must presumably not be too great; otherwise the precipitated *protein would be washed away before it was built up into casts.* Thus for example, in other medical conditions where casts are formed in the renal tubules of a previously normal kidney, the casts date from a period not only of gross proteinuria but also of severe oliguria due to shock or pyrexia.

The various factors involved in cast formation are related to the function of the whole kidney, including the medulla and intermediate zone. In U.P.A. these latter regions probably retain an uninterrupted blood supply, but they may nevertheless not be functioning normally during the first 12 hours after the U.P A.. There are thus two possible causes for the virtual absence of casts in the collecting tubules during the first 12 hours: the glomeruli may not be *producing any filtrate at that time, or, if they are doing so, the tubules may* be unable to concentrate it. The anuria or severe oliguria during this period

appears to be due to the temporary general disturbance of renal function, and cannot be ascribed to cast formation.

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factors discussed in the next section, these casts may produce very serious effects in two ways. Firstly they must give rise to a considerable degree of obstruction to the flow of urine down the tubule, though not necessarily a complete occlusion. Some types of cast are very solid, while others have a loose granular structure; some occupy the whole lumen, while others are relatively narrow. Secondly, at the point where they lie in contact with the wall, they produce a local pressure damage of the epithelium; this may range from severe crushing to complete necrosis Any lesion in this segment is of

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compared with the insulation around a wire carrying a high-tension electric current. When a series of gaps are made in the epithelium of the collecting tubule, there is no obstacle to the escape of urine from the tubule into the medullary connective tissue Thus the urine is short-circuited back into the bloodstream Even a partial obstruction of the tubule by casts would accelerate the leakage The accumulation of large monocytes in the intermediate zone, and their later replacement by lymphocytic foci, always follows the deposition of casts in medullary tubules, and is presumably related to the escape of urine into the interstitial tissue of the medulla

These remarks apply specifically to those cases of U.P.A where the essential renal lesion is the formation of collecting tubule casts, and there is no serious cortical damage In certain cases of proximal convoluted tubule necrosis and of R C N, there is considerable cast formation in the collecting tubules. These casts may add seriously to the ren[illegible]
which have remained relatively [illegible]
overshadowed by the dominant [illegible]
where collecting tubule casts and R.C N are combined in the same kidney, it is important to differentiate clearly between the two conditions, as has been emphasised recently by Young (1949) and Smith (1949)

ACUTE ANURIA AND CAST FORMATION IN GENERAL MEDICINE

Acute renal failure lasting several days occurs not only in obstetric conditions but also in a wide variety of other medical conditions, such as incompatible transfusion, blackwater fever, Weil's disease, crush kidney, etc. The precise cause of the oliguria or anuria has been discussed by many authors, including Bell (1937), Bywaters and Dible (1942), Oliver (1945), Maegraith,

Havard and Parsons (1945), Lucké (1946), Mallory (1947), *van Slyke* (1948), Muirhead and Hill (1948), Lewis (1949), O'Donnell (1949), Dible, Bull and Darmady (1950), French (1950), Smith and Muirhead (1951), Koslowski (1951), Gaberman et al. (1951). In these conditions casts are usually formed in the distal convoluted or collecting tubules, but they do not develop until about 12 to 24 hours These casts are of two main types: (*a*) those which are due to the sudden liberation into the plasma of some protein such as haemoglobin or myoglobin which is filtered through the normal glomerulus, (*b*) those consisting of ordinary plasma proteins which have escaped into the tubule because of acute damage to glomeruli; e.g. the albuminuria casts of U.P.A.

As discussed in the preceding section, there are two problems in these acute renal failures: *firstly the cause of the anuria during the first day, and secondly* the cause of the anuria during the subsequent week or two.

There is nearly always an initial period of severe shock or pyrexia, frequently associated with intravascular haemolysis. The oliguria or anuria during this phase may be due to some reduction in the renal bloodflow, or to an absence of filtration as a result of low pressure in the glomeruli, or to some functional disturbance in the renal tubules allowing almost complete reabsorption of the filtrate. The part played by these various factors is not clear. Certainly any reduction in renal bloodflow cannot be of a very severe grade, because there is usually no histological damage to the most sensitive part of the parenchyma, i.e. the proximal convoluted tubules. The anuria during this particular time *must therefore be considered to be a functional rather than a structural* disorder.

The other main problem is the mechanism of the oliguria or anuria during the second stage, i.e. during the week or two after the first day. Debate on this topic hinges on the question of whether the casts in the *collecting tubules* constitute the important pathological change, or whether the continued renal failure is due to some prolonged functional disturbance which prevents the formation of urine.

Much of the recent discussion in the literature rests on the statement by several authorities that the casts in the distal convoluted or collecting tubules are never sufficiently large or numerous to interfere with renal function. While this may be true in some cases, there are certainly very many kidneys where the casts appear to be of great importance, both by the pressure-damage they produce on the epithelium and by the obstruction of the lumen of the tubule. The mechanism of these effects has been sufficiently discussed in the preceding *section* The question of whether there are enough casts to produce these effects requires a careful assessment of the number of tubules which contain casts. Three points must be borne in mind. Firstly, there may be long casts throughout much of the collecting tubule, or only short ones in occasional places. The *latter condition is important; the occlusion of a collecting* tubule at

a single point is potentially just as harmful to the nephron as the more extensive obstruction. A cast which obstructs one of the main collecting tubules will affect the urine flow from the large group of related nephrons. Secondly, no valid opinion can be given unless the histological sections include not only the cortex but also the whole medulla to the tip of the pyramid. Thirdly, thin paraffin sections may lead to an underestimate of the number of casts; thick frozen sections are of much more value. The method of dissection of nephrons employed by Oliver (1945) demonstrates the situation and number of the casts very clearly, but it is technically not so easy. The true size of the individual casts can be judged in thick frozen sections more satisfactorily than in paraffin sections, because the casts often shrink a great deal during paraffin embedding.

When the kidney is studied carefully in this way, there can be no doubt that in many cases the cast formation is quite sufficient to give rise to the oliguria or anuria and that it is therefore unnecessary to postulate any additional factors, though the existence of such factors is not thereby disproved. On the other hand it must be agreed that there are some cases where the anuria cannot be satisfactorily explained by the few casts present. In this second group of cases there must be some other particular factor causing the anuria. Nevertheless, it is important not to assume that this particular factor is the significant one in all cases of anuria, whether or not casts are present, and that the casts themselves may always be ignored in the aetiology of the anuria. The concept that all these cases of anuria must have a common aetiology would have an attractive simplicity, but unfortunately it is not in agreement with the clinical and histological data. It does not appear justifiable to put into one common group: cases of toxic proximal convoluted tubule necrosis due to mercury poisoning, cases of gross haemoglobin cast formation due to incompatible transfusion, and cases of R.C.N or other ischaemic damage to the cortex resulting from U.P.A.. The fact that the present treatment of all these conditions is the same should not be allowed to obscure the wide differences of aetiology and pathology.

In the cases where the anuria can not be accounted for by the casts or by any more severe structural change in the kidney, it is not easy to give a satisfactory explanation for the continued anuria. One group of authors maintain that there is a serious dysfunction of the distal convoluted or collecting tubules, and that this is evidenced by histological changes in the epithelium of those segments. In the cases personally observed, these changes have been related either to casts or to sites where it is clear that casts have been present previously. Nevertheless certain authorities are satisfied that "tubular bursts", which permit leakage of urine into the interstitial tissue or neighbouring blood vessels, can occur without any relation to cast formation (Dunn, Gillespie and Niven, 1941; Darmady, 1950, Oliver, MacDowell and Tracy, 1951).

An alternative explanation of the prolonged anuria is that it is due to a continuance of those factors which caused the anuria during the first 12 to 24 hours. This is sometimes accounted for by a "renal anoxia" resulting from a renal ischaemia. The cause of such a prolonged renal ischaemia is obscure; one of the many possible explanations is that the presence of the casts might produce a reflex inhibition of renal bloodflow. There is some evidence suggesting that the renal bloodflow may in fact be reduced for several weeks (Bull, Joekes and Lowe, 1950). Nevertheless it does not appear that the renal ischaemia can be of a very severe degree, because it does not produce any histologically recognisable ischaemic damage to the kidney. Furthermore, if it be accepted that in most cases the anuria is due to a moderate degree of renal ischaemia, it might reasonably be expected that in occasional cases the ischaemia would happen to be more severe, and would thus produce either necrosis of proximal convoluted tubules or the various grades of R.C.N.. In other words, there should be some parallel to the series of lesions which occurs after U.P.A., and which is due to various gradations of renal ischaemia There is evidence that such a series does occur rarely in a few conditions listed in Chapter X, but it is not found in the other anurias and, in particular, not in those where an abnormal protein is being excreted by normal glomeruli.

The proximal convoluted tubules do not usually show much dilatation in cases where casts are present in the distal convoluted and collecting tubules. This is sometimes interpreted as evidence that the lower segments are not obstructed Such an inference can not be accepted as valid. Even in the normal kidney it is difficult to assess the hydrodynamic conditions in the various parts of the nephron. On the ordinary theories of renal function, the proximal convoluted tubule must be carrying a volume of fluid a hundred times greater than the distal convoluted tubule of the same nephron, though this could not be deduced from the diameter of the lumen of the two segments in histological sections The pressure gradient inside the lumen must be influenced very considerably by the site of absorption of the fluid, but the details of this are not yet known In view of the difficulty of histological assessment of the pressures and volume flows in the tubule in ordinary physiological conditions, no valid interpretations can be given of the presence or absence of dilatation of the proximal convoluted tubules in pathological conditions.

HAEMOGLOBIN CASTS IN U.P.A.

Despite the rather extensive internal haemorrhages of U.P.A., there is little or no haemoglobinaemia, and consequently no haemoglobinuria. Haemoglobin casts are thus not a characteristic feature of the U.P.A. kidney, and there was not a single example in the present series. Certain other authors have reported the occurrence of haemoglobin casts following U.P.A., but there may have been other factors operating in these cases (Young, 1942*b*, Case 2;

Paxson, Golub and Hunter, 1946, Case 1; Mauzy and Donnelly, 1949, Case 2; MacGillivray and Govan, 1952, Cases 2 and 5). For example, Mauzy and Donnelly's case had been given several transfusions; biopsy at 5 days showed haemoglobin casts in the lower portions of the nephrons. The patient recovered. Both of the cases of MacGillivray and Govan were given blood transfusions.

Haemoglobin casts may develop in a variety of conditions in pregnancy unrelated to U.P.A.. Incompatible transfusions and other intravascular haemolyses frequently produce haemoglobin casts Similar casts are seen following certain abortions; the intravascular haemolysis being the result of injections of soap solutions, ingestion of quinine, or infection by Cl. Welchii (Terplan and Javert, 1936, Chabanier et al., 1936, Case 2; Bratton, 1941, 8 cases; Young, 1942*a*, O'Sullivan and Spitzer, 1946, Case 1; Young and Walker, 1947, O'Donnell, 1949, Cases 1, 2 and 3, Wyatt and Goldenberg, 1950, Cases 1, 2 and 3) A biopsy on a patient with an abortion followed by oliguria was reported by Chabanier et al. (1936, Case 1) There were haemoglobin casts in the distal convoluted tubules in the cortex. Haemoglobin casts are also formed in some cases of eclampsia, probably in association with very extensive haemorrhages in the liver White (1919) recorded a biopsy on a patient (L B) with post-partum oliguria, and has permitted us to report from his original slides This patient had eclampsia at 24 weeks in her first pregnancy. Biopsy on the 11th day of the puerperium showed numerous haemoglobin casts occupying the distal convoluted tubules in the cortex. The medulla was not included in the biopsy. The patient recovered.

HYALINE DROPLETS AND COLLOID DEGENERATION

These two lesions develop at about the same time, and appear to be aspects of the same disturbance They depend on a sequence of factors: (*a*) the initial ischaemia disturbs the filtration mechanism of the glomeruli, and at the same time damages the tubular epithelium; (*b*) when the blood subsequently circulates through the area, there is a flow of protein-containing filtrate down the tubule, and the damaged tubular epithelium retains sufficient function to absorb some of this protein.

[illegible]

plications, the lesion probably disappears within a couple of days. With more severe damage, the epithelium accumulates protein in a more diffuse manner and undergoes colloid degeneration This process also requires a reflow of blood lasting about 12 hours to reach its full development

The amount of the proteinuria may vary from one nephron to another.

Sometimes a severely damaged glomerulus may communicate with a relatively undamaged proximal convoluted tubule which has received some capillary blood supply from the neighbourhood; the reverse condition may obtain. This may be one of the reasons why the histological picture of colloid degeneration is so varied.

In a few cases during the first day, colloid degeneration is found in a broad zone around areas of early R.C.N. or of proximal convoluted tubule necrosis. In other cases at this time, there is no sign of colloid degeneration or even of hyaline droplet change at this site. This is difficult to explain, as it might reasonably be expected that an area of severe ischaemia would always have a marginal zone around it where there was partial ischaemia. A possible explanation is that such a zone of partial ischaemia would have its bloodflow from anastomoses with neighbouring capillaries; this would not be sufficient to produce any glomerular filtration, and thus the tubules would not be presented with albuminuric filtrate.

In the late cases the absence of colloid degeneration around the live margin zone of an area of R.C.N. is of no significance; if any such process had occurred in the early stages, the tubule would by this time have recovered.

COLLOID NECROSIS

The occurrence of colloid necrosis (i.e. necrosis of tubules which have previously undergone some degree of colloid degeneration) brings up for consideration a further concept of general pathology which is applicable to all the renal lesions It has been concluded that the formation of hyaline droplets and simple colloid degeneration indicates that the tubular epithelium though damaged is still alive and is able to reabsorb, from the glomerular filtrate, protein which is accumulated in the epithelial cells.

The problem [illegible] these tubules should die and [illegible] protein in the cytoplasm is [illegible] is basically plasma-protein, and it is harmless when it is present as hyaline droplets. The more reasonable explanation is that the late necrosis is the result of a late ischaemia. When tubules have already been seriously damaged as a result of spasm at glomerular level, and during the subsequent reflow have undergone a severe colloid degeneration, a brief recurrence of the spasm at the same site a few hours later would be sufficient to cause their death. That such a recurrent spasm at glomerular level does sometimes occur is shown in Case 36, where there were many areas of severe colloid degeneration and of early colloid necrosis, but in addition the glomeruli in a few minute areas showed early necrosis and thrombosis.

The concept that spasm may recur at glomerular level during the first few

hours raises the whole problem of whether spasm at that site may frequently be intermittent. The present histological material does not give a conclusive answer, but we are much attracted by the idea that the lesser lesions, such as hyaline droplet formation and colloid degeneration, may usually be due to intermittent spasm; the relatively long time required for their development would then be due to the gradual building-up of the effects of the intermittent ischaemia.

INTERMEDIATE ZONE COLLOID CASTS

This lesion appears to be almost peculiar to the U P A kidney, though it occurs in only about one-third of the cases In contrast to the delay in the formation of ordinary protein casts in collecting tubules, the colloid casts in the intermediate zone tubules can be fully developed as early as 6 hours

These casts appear to have a very high protein content, including possibly a large amount of globulin On the basis of the ordinary processes of renal physiology, it might reasonably be considered that the colloid material had filtered through the glomeruli and become deposited in these segments of the nephron. There are however some difficulties in this explanation.

(*a*) In the few cases where the colloid is seen in glomerular capsules, it is not seen in the proximal convoluted tubule any further down than the first two or three loops Beyond this point there is a big gap until the colloid casts are met in the spiral segments

(*b*) In early cases, the colloid casts can be seen filling the spiral segments of the proximal convoluted tubules in the intermediate zone and also filling the broad ascending limbs of Henle, but with no recognisable colloid in the narrow loops of Henle which connect those two segments.

On the other hand, this "gap" is not invariable; there are many examples of colloid casts continuing from the spiral segments down through the narrow loops of Henle in the medulla and then up again into the broad ascending limbs in the intermediate zone. In the cases where the cortex is not affected by R.C N , these casts may sometimes be seen continuing from the broad ascending limbs up to the distal convoluted tubules but no further, or they may sometimes continue in lesser amount as far as the collecting tubules

(*c*) The explanation strikes another difficulty in some of the cases of gross R.C N. The colloid casts could not result from filtration after the R C.N had developed. [illegible]

delicate lesions which occurred in the very early stages of the R.C.N can still be identified easily in the late stages. In fact, neither in the early stages of gross R C N. nor in the late stages, are there any colloid casts in the distal

convoluted tubules in the cortex. Nevertheless, in at any rate the late stages of gross R.C.N., every tubule in the intermediate zone and every collecting tubule in the medulla may contain these casts.

One possible *explanation of these facts may be that the formation of colloid* casts is dependent on the active function of the tubular epithelium, and that the peculiar localisation to the intermediate zone may be related to alterations in the blood supply near the lower margin of the ischaemic cortex. It is certainly conceivable that, even in cases of incipient R.C.N., some dilute colloid might pass along the nephron and be deposited as a gel only in segments with well-functioning epithelium. The distal convoluted tubules in the cortex can not be considered to have normal function in the initial stages of R.C N.

The only possible alternative explanation is that there is a direct secretion of this colloid by the epithelium of the affected tubules. There are pathological analogies to suggest such an explanation; in particular the formation of almost identical colloid casts in the lumen of isolated segments of renal tubules, such as is seen in certain types of chronic nephritis. It must be admitted that the *answer to this problem remains obscure.*

In the description of colloid casts in Chapter IV, it was pointed out that, in the cases without R.C.N., the formation of colloid casts in the intermediate zone is commonly associated with the occurrence of colloid degeneration and colloid necrosis in the proximal convoluted tubules in the cortex. There is, however, nothing to show that these conditions are aetiologically related. The use of the adjective "colloid", both in the title of the tubular lesions and in the title of the casts, is purely descriptive and carries no further implication.

PROXIMAL CONVOLUTED TUBULE NECROSIS

The site of the operative spasm is at glomerular level, as is shown by the nephronic distribution of the lesions. The spasm lasts about 3 hours and, in *an uncomplicated case, is followed by the re-establishment of a permanent* bloodflow, which allows the development of the necrosis-changes and the subsequent repair of these tubules. The tubules always seem to have been killed outright; there are no cytoplasmic changes to suggest that the spasm has been intermittent.

In the early cases, only occasional proximal convoluted tubules are obviously necrosed. The adjacent tubu
it is impossible to determine whether tl
have recently been killed but have not
develop *necrosis-changes. Subsequently the number of nephrons* showing obvious necrosis tends to increase up to about 18 hours or so. There are two possible explanations: (*a*) that the spasm may begin in different nephrons at different times within about the first 12 hours, (*b*) that the reflow of blood may

begin at different times and may be of various degrees of efficiency.

The minimum period of reflow of blood necessary to produce unequivocal necrosis-changes in the nuclei and cytoplasm is about 2 or 3 hours, as judged by kidneys examined 6 hours after the U.P.A.. Sleeve-separation is not seen until after about 6 hours' reflow. Nuclear staining is lost after about 12 to 18 hours' reflow.

Proximal convoluted tubule necrosis is a specific entity, and in many cases develops without any other complication whatsoever. Nevertheless it is clearly related to other lesions. At the lower aetiological range there are cases where the kidneys show a mixture of this lesion and colloid degeneration; the latter being interpreted as occurring in those nephrons where there has been an earlier relaxation of the spasm At the other end of the aetiological scale are the cases where, though most of the nephrons have simple proximal convoluted tubule necrosis, the spasm in occasional glomeruli has lasted long enough to produce benign glomerular thrombosis.

GLOMERULAR THROMBOSIS AND SMALL FOCI OF R.C N

When the spasm at glomerular level has lasted for some time estimated at about 4 to 6 hours, serious damage has occurred to the endothelium of the glomerular capillaries, but the walls of these vessels are not killed unless the ischaemia has been of rather longer duration. When the bloodflow re-opens through the damaged capillaries, fibrin thrombi are laid down in their lumen. These thrombi may be of various types, dependent on the duration of the initial ischaemia and on the efficiency of the recirculation of blood

The mildest type is that which has been referred to here as benign glomerular thrombosis. The loose strings of fibrin thrombus, which develop in the lumen of the capillary loops, could certainly be formed in a few minutes As the bloodflow continues, a more hyaline type of thrombus is built up around the original fibrin threads; it lies free in the lumen without obstructing the bloodflow, so that the glomerulus survives. A similar thrombus may develop in the stalk afferent vessel; the essential difference seems to be that the spasm has been at the root of this vessel instead of at the roots of the capillary loops.

If the spasm at glomerular level has lasted a rather longer time, the resultant glomerular damage is more severe When the circulation re-opens, the stalk afferent vessel becomes dilated, and a solid mass of adherent thrombus is gradually built up in it The arrest of the bloodflow leads to death of the glomerulus, if this structure has not already been killed by the first ischaemia The lesion now fulfills the criterion of focal R.C N.

Sometimes this solid thrombus is present only in the stalk afferent vessel, but occasionally it spreads down the centre of the lumen of the afferent arteriole, this is of importance in that it suggests that the arteriole may have

been in partial spasm. In the most severe cases of focal R.C.N., the arteriole is dilated, its wall shows necrosis-changes, and it usually becomes plugged by solid thrombus.

The development of stasis in glomeruli may be the product of two different mechanisms. When blood flows into a dead glomerulus, the plasma may escape, leaving the red corpuscles as a packed mass in the capillary loops. This effect would be precipitated or enhanced if the spasm in the afferent arteriole were to relax at a time when the efferent arteriole happened to be in spasm. There is no direct evidence to prove either of these factors.

The stasis is seen in a few glomeruli at about 14 hours. Subsequently there is a spread to involve further glomeruli up to about 20 or 24 hours, but not after that time. It is possible that stasis in some of the glomeruli may have resulted from a single sequence of ischaemia and reflow. Nevertheless, stasis sometimes occurs in glomeruli which show benign capillary or stalk thrombosis. This thrombosis occurs during the reflow after the first ischaemia, and must therefore precede the stasis. In addition, it could not possibly occur after the stasis, at a time when the capillaries are filled with stationary red corpuscles, as is explained in the Chapter on the early stages of R C.N.. In these glomeruli it must be accepted that there has been a double sequence of ischaemia and reflow

Parenchymal changes. In the areas where benign glomerular thrombosis has occurred, the ischaemia has always continued long enough to kill the proximal convoluted tubules, though not long enough to kill the distal convoluted tubules or the intertubular capillaries. In the intervening areas there is much proximal convoluted tubule necrosis and lesser tubular damage.

When solid thrombosis of a stalk afferent vessel or arteriole has occurred, or when stasis has developed in a tuft, this glomerulus is dead, and the condition is a focal R.C.N.. This may involve only a single glomerulus, or it may involve a small group of adjacent glomeruli. In the latter case, the focus of R C.N. is recognisable to the naked eye, but it is still sufficiently small for the distal convoluted tubules and the intertubular capillaries to be kept alive by the collateral capillary circulation. This circulation is poor, so that the centre of these larger areas of focal R.C.N. consists of partial survival zone, and the repair of the proximal convoluted tubules here is delayed.

It is not clear why, in cases following U.P.A., focal R.C.N. involves only scanty and scattered groups of glomeruli, despite the ample evidence among the less severe lesions that spasm at glomerular level can affect most of the nephrons.

CONFLUENT FOCAL R.C N

This condition is basically similar to the focal R.C.N. which follows U.P.A.. The main difference is that, instead of there being only occasional scattered

lesions, the foci of R C.N. occur in very large numbers and may become confluent in extensive areas of the cortex

The common type seems to be of gradual development The lesions are indicative of a series of spasms at glomerular level, beginning in different glomeruli over a period of several days. The spasm may vary in duration from a few minutes up to about 6 hours, and probably recurs at intervals in the same tuft. It is succeeded by a reflow of blood through most of the glomeruli It is a striking feature of this condition that many of the glomeruli have thrombosis or stasis, but there are enough undamaged or only partially damaged glomeruli to allow adequate through-circulation to the cortex, so that the parenchymal lesions pass through their necrosis-changes at the same rate as in simple proximal convoluted tubule necrosis

In the less common type of confluent focal R.C N., the lesions develop almost simultaneously instead of serially. The spasm continues, probably intermittently, in the glomeruli long enough to kill many of them. When the reflow occurs, much of the bloodflow to the cortex is arrested rather rapidly as a result of glomerular stasis and thrombosis. Nevertheless, even in the most severely damaged glomeruli, this reflow continues long enough to produce solid thrombosis of platelet type in the stalk afferent vessels. There is however no spasm in the intralobular arteries, so that blood can pass through the least damaged glomeruli, and is able to provide a moderate circulation through the cortex In areas where this bloodflow is adequate, the necrosis-changes of the proximal convoluted tubules progress at a fairly normal rate, and there is no necrosis of distal convoluted tubules and no dehaemoglobinisation in those glomeruli which have suffered stasis On the other hand, where the lesions in all the glomeruli of a large area have been so severe that the reflow is arrested, there is delay in the necrosis-changes of the proximal convoluted tubules, and necrosis occurs in the distal convoluted tubules

The spasm remains cha[illegible]
very occasional examples [illegible]
of the arterial tree do n[illegible]

The clinical information about these cases is usually inadequate to establish the exact time of onset of the renal damage, because the R C N is not a sequel to any dramatically sudden condition such as U.P A. The estimation of the duration of the renal damage thus depends on a histological assessment of the age of the oldest acute lesions in the kidney.

Dunn and Montgomery (1941) recorded eight cases of R.C N. in non-pregnant patients and arranged them in a series, beginning with three cases of confluent focal R C N of about 2 to 3 days' duration, and following with five cases of R C.N. of arterial type and of longer duration. They suggested that this indicated a sequence of events: the condition described here as confluent focal R.C.N was the initial lesion; after a few days it was

followed by a secondary degeneration and thrombosis of the arteries, giving finally the classical picture of gross R.C.N.. There is no evidence to support this theory of a long-delayed arterial degeneration. The present cases of confluent focal R.C N. several days old have undamaged intralobular arteries, whereas the cases of gross R.C.N. have necrosis and thrombosis of arteries at 36 hours. Furthermore, any long delay of 4 days or more in the onset of spasm or thrombosis in the artery would lead to necrosis of regenerating tubules, a condition which is never seen. It appears therefore that their Cases 1, 2 and 3 are best considered, not as early stages of their cases of patchy and gross R C N., but as examples of a different variety of ischaemic lesion (confluent focal R.C.N.) which would have progressed along its own line without further involvement of the arterial tree.

MINOR, PATCHY AND GROSS R.C.N.

The initial spasm and first reflow. In areas of extensive R.C.N., the initial spasm at glomerular level affects all the nephrons in the area. It seems to begin at about the same time in all the glomeruli.

The duration of the spasm appears to be fairly long, as judged from the lesions which are revealed during the subsequent reflow. This reflow produces fibrin thrombi in some of the glomeruli and intertubular capillaries; the damage to this endothelium indicates that the initial ischaemia has lasted about 4 to 6 hours There is no clear evidence that stasis or other severe glomerular damage ever occurs at this stage; it is therefore unnecessary to postulate a longer initial spasm During the reflow, some albuminous filtrate passes into the proximal convoluted tubule Almost every proximal convoluted tubule shows necrosis-changes; the death of these structures indicates that the initial ischaemia lasted for at least 3 hours. Only a very occasional proximal convoluted tubule shows early colloid degeneration, proving that in these particular nephrons the initial spasm was not long enough to kill the tubule outright. There are, however, never any tubules so slightly damaged that hyaline droplets can form in them. The distal convoluted tubules may be killed at this stage. Even if they remain alive, they are seriously damaged so that they are incapable of producing casts in their lumen.

When the reflow begins, it does so in a very patchy and nephronic manner. The general picture suggests that the reflow of blood is not of good volume anywhere, and it is possible that the bloodflow may be impeded somewhere, either in the arteries or in the glomeruli. The reflow must terminate simultaneously throughout each affected segment of the cortex, because it is arrested in the intralobular artery.

The arterial spasm and second reflow. At about 6 to 12 hours the circulatory condition undergoes a great change, owing to the development of operative

spasm at some point in the intralobular artery, with a resultant complete ischaemia of all structures beyond the site of the spasm. The site of the spasm varies considerably from case to case; this accounts for the difference in extent of minor, patchy, and gross R.C.N.. In any individual kidney however, the spasm tends to occur at about the same level in most of the intralobular arteries, and probably develops at about the same time in these arteries There are some individual variations, so that one artery may be in severe spasm while its neighbours remain open. Where the arteries have not been in spasm, the area shows merely proximal convoluted tubule necrosis with, perhaps, a few points of focal R.C.N.

The arterial spasm relaxes very much earlier in the small arteries, which are involved in minor R.C N , than in the large arteries, which are involved in gross R.C N.. The times are possibly about 10 or 12 hours in the former, and 24 to 36 hours in the latter In a single kidney there is probably a range of a few hours between the time of relaxation of one artery and that of its neighbour. As a result, the kidney with gross R.C N. at 36 hours has blotches of dark and light red on the cut surface; the blood in some areas is dehaemoglobinised, and in other areas not.

The second reflow is terminated fairly quickly by the development of thrombosis and stasis. After this time the entire area is permanently ischaemic

No explanation can be offered for the peculiar fact that in confluent focal R C N , where there is very extensive severe spasm at glomerular level, the spasm does not transfer into the arteries subsequently. After U P.A , on the other hand, in every case where there is extensive spasm at glomerular level, which in theory could give rise to a confluent focal R C N., the spasm transfers to the main intralobular artery and produces, instead, a gross R C.N

IDENTIFICATION OF THE EARLY STAGES OF GROSS R C.N.

There are two conditions with which the early stage of R C.N may be confused:—the early stages of very extensive proximal convoluted tubule

nephrons relatively evenly. At 3 hours the vascular disturbance is practically identical in all of them The differentiation of these various conditions depends on their subsequent course.

In extensive proximal convoluted tubule necrosis, the spasm lasts about 3 hours and then passes off, so that a good bloodflow is established throughout the area Necrosis-changes in the dead tubules progress steadily from this time onwards In the more severe varieties of this condition, there may be widespread benign glomerular thrombosis, but there is clear evidence of a permanent re-establishment of bloodflow.

In the special variety of confluent focal R.C.N., the parenchymal changes are severe and there is extensive and very striking damage to glomeruli, but here again the subsequent course of the necrosis-changes in the tubules indicates a continuation of some bloodflow through the area.

In gross R.C.N. *the ischaemia is very widespread* and produces severe and very extensive damage. The reflow is relatively poor, so that at about 6 or 8 hours the glomerular lesions are very much less prominent than in a confluent focal R.C.N. The development of the arterial spasm arrests this first reflow, and, as a result, there is no further development of the histological changes in *the kidney, apart from the progress of the dissociation of the epithelium of the* distal convoluted tubules and the beginning of dehaemoglobinisation. At this period, the appearances of the kidney in gross R.C.N. become clearly different from those of the widespread nephronic lesions.

DISTRIBUTION OF LESIONS IN R.C.N.

In gross R.C.N. and in patchy R.C.N. there are always a number of radiating bands of live tissue traversing the cortex. In addition a variable number of subcapsular and juxtamedullary nephrons remain alive. These *appearances are related to variations in the distribution of the arterial spasm.*

(*a*) In some places the operative spasm which produces the R.C.N. begins about half-way out along the intralobular artery, and all the branches of the artery proximal to this point remain open. As a result, a broad wedge of tissue free from R.C.N. is left projecting up from the juxtamedullary region into the deep cortex. This gives the characteristic serrated lower edge of the necrosed area.

(*b*) In a few places the operative spasm does not involve the main trunk of the intralobular artery nor its juxtamedullary branches, but all the branches further out are in spasm, apart from a few small terminal branches to nephrons under the capsule, and sometimes also a branch to the renal capsule itself (More and Duff, 1951). As a result, there is a small wedge of live parenchyma pointing inwards from the capsule into the cortex. The blood in this arterial trunk remains in true circulation because of the distal outlet to the capsule; *the arterial wall thus remains alive and there is no thrombosis.*

(*c*) In various places these two processes are associated in the same intralobular artery, so that there are two wedges of live tissue pointing towards each other across the area of R.C.N.. If the wedges are larger, their apices are fused; an extension of this process gives rise to the columns of live tissue from capsule to medulla which are seen in occasional places in *even the most severe* cases of R.C.N.

(*d*) Further developments along the lines described in para.(*a*) reduce the area of affected parenchyma so that the R.C.N., though gross in general type, involves only the outer half of the cortex. On the other hand, when a large

number of isolated intralobular arteries are spared along their whole length, as described in para.(*b*), the result is the streaky type of patchy R.C.N. involving nearly the whole depth of the cortex (Fig. 62). A combination of the two processes gives the ordinary type of patchy R C.N. (Fig. 61).

NECROSIS OF ARTERIES

The spasm in the artery leads to death of all the distal part of the arterial tree. When the second reflow occurs, the subsequent developments are (*a*) the occurrence of dilatation and certain special necrosis-changes in these dead arteries, (*b*) the occurrence of thrombosis in them.

When the operative spasm passes off, blood re-enters the distal segment of the arterial tree, at presumably the ordinary arterial pressure. The arteries immediately become dilated. Such dilatation could occur if the arterial walls were merely paralysed as a result of the ischaemia, but it appears that they are, in fact, dead at this stage

The early lesions which develop in these dead and dilated arteries are probably related to the re-entry of blood into the lumen under pressure The muscle cells of the media disintegrate, and the internal elastic lamina is stretched or broken. Red blood corpuscles or polymorphs irrupt into the media. This latter change is observed mainly in small arteries but not in large ones; the reason for the difference is not clear. These lesions occur very soon after the *blood re-enters the artery, and may be quite prominent as early as 12 hours.* The subsequent developments in the arterial wall are essentially the ordinary necrosis-changes of dead tissue; these progress at a rate dependent on the proximity to circulating blood.

This explanation of the necrosis of the arteries is not in accordance with some of the views given in the older literature Navasquez (1935) and Gáspár (1938) are of the opinion that the necrosis of the arteries is the primary lesion in R C N , and that stasis in these necrosed arteries then leads to the ischaemia of the parenchyma The fact that the ischaemic lesions of the parenchyma precede the necrosis of arteries renders this view untenable Other authors, listed by Duff and More (1941), maintain that not only is the necrosis of the artery the primary lesion, but that the necrosis can actually be seen spreading in the walls of arteries outside the area of *R C N.* several days later *As* will be explained in the last section of the present Chapter, this fibrinoid change is merely a late local reaction, and is quite unrelated to the necrosis of arteries which occurs in the developing stages of R C.N.

Dunn and Montgomery (1941) postulate that the ischaemia develops as a result of primary stasis at glomerular level, and that the arterial lesions are purely secondary to this arrest of the bloodflow at the periphery This explanation does not account for the absence of arterial lesions in the [illegible]

of focal R.C.N., *and particularly in the* cases of confluent focal R.C.N.. Furthermore, in very many cases the glomerular lesions do not develop until 14 to 24 hours, and appear to occur simultaneously with the arterial lesions.

THROMBOSIS OF ARTERIES

The various types of thrombosis are clearly related to different local aetiological disturbances.

SOLID THROMBOSIS IN SMALL ARTERIES

Under this heading will be considered the formation of the very solid homogeneous or slightly granular thrombus which occludes the small arteries in minor R.C.N , and also the arterioles and stalk afferent vessels in focal R.C.N.

This thrombus corresponds to what is usually described as a platelet thrombus, and it must be laid down in blood which is in circulation in the vessel The total amount of platelets which would be required to build up this thrombus represents a volume of blood enormously greater than the actual content of the vessel It is therefore necessary that the blood be either in circulation through the artery, or in pulsating to-and-fro movement from the healthy part of the artery If a through-circulation does occur for a time, it must certainly cease if and when stasis occurs in the glomeruli.

Various factors must be taken into consideration in any explanation of this thrombosis:

(*a*) The process occurs only in small vessels, and there has always been a continuing bloodflow in areas in the immediate vicinity. There must therefore have been some diffusion of oxygen into the region of the dead artery.

(*b*) The artery is certainly dead at about the time the thrombosis occurs, because it has been dilated by the inflow of blood, and its media is infiltrated with blood cells Nevertheless it seems that the artery has been dead only a short time, because the thombosis is seen as early as 14 hours.

The fact that the artery is only recently dead, and has some oxygen supply *from the neighbourhood*, gives *different local* biochemical conditions from those in an artery which has been dead a long time. As a result, there is no rapid formation of loose fibrin thrombus, and the circulation continues in the artery long enough to allow the development of a platelet type of thrombus.

The duration of the spasm required to kill a small artery is *less than 14 hours*, because by this time occlusive thrombus has been built up in cases of minor R.C.N.. It may therefore be presumed that a period of ischaemia of perhaps 8 to 12 hours is lethal to these small arteries. There is no reason to believe that large arteries are able to withstand any longer period of ischaemia.

THICK MURAL AND TRELLIS THROMBOSIS

This condition is seen most typically in the cases of patchy R C.N., where the spasm has occurred about midway along the intralobular artery.

The thick mural thrombus has the less complicated development, and may therefore be considered first. It consists mainly of fibrin; the total amount of this fibrin could only be deposited from a relatively large quantity of blood. It is therefore necessary to postulate that there is some flow of blood. There may be a through-circulation for a short period of time; a circulation which would also account for the occasional occurrence of thin mural thrombosis in the more distal parts of the arterial tree, and of stasis in the glomeruli. Alternatively, the blood in the artery may remain fluid for some time and have a to-and-fro movement transmitted from the blood in the healthy part of the artery, so that interchange of plasma can occur

Trellis thrombus is essentially a variant on the thick mural type, forming in a wider part of the artery, and closer to the healthy part of the artery which contains normally circulating blood. The columns of the trellis thrombus appear to consist of platelets and condensed fibrin, and correspond in general structure to the lines of Zahn which are formed in thrombosis of vessels elsewhere in the body The bases of the columns are attached to the intima of the artery; the columns themselves build up a trellis across the lumen. The total amount of platelet material is such that the thrombus represents a considerable amount of blood It must therefore be accepted that the blood in this part of the artery remains in free communication with the blood in the live portion of the artery for some time, possibly a few hours During this time the blood remains fluid and in to-and-fro movement, gradually building up the columns of the trellis, and coating them in places with polymorphs At the end of this period, the trellis has produced considerable obstruction of the lumen, and the blood in the interstices, consisting mainly of packed red corpuscles, undergoes simple coagulation These red corpuscles disintegrate about a day later Further blood then seeps into the spaces of the trellis and coagulates; the red corpuscles disintegrate in turn This process is repeated at intervals for several days, so that, at any time during the next few days, the spaces of a trellis thrombus may contain fresh red corpuscles, dehaemoglobinised red corpuscles, or only a trace of debris

Trellis and thick mural thrombi have not been seen earlier than 36 hours, which is very late as compared with the occurrence of thrombosis in small arteries in minor R.C.N. There are various possible explanations for the delay:

(*a*) The operative spasm in the artery in patchy R C.N may not begin until perhaps 6 or 8 hours after the U P A In these cases necrosis-changes can be seen in the proximal convoluted tubules, which is evidence of a first reflow of blood. It appears therefore that patchy R C N has the double sequence of

ischaemia and reflow. By contrast, in minor R.C.N. it seems that the two spasms are telescoped into one shorter single sequence.

(*b*) The operative spasm continues longer in these large arteries than in the small ones that are involved in minor R.C.N.. The spasm in these smaller arteries, in turn, lasts longer than the spasm at glomerular level in focal R.C.N. or the lesser lesions It seems probable that the spasm in patchy R.C.N. may last 12 to 18 hours.

(*c*) The arteries where these trellis and thick mural thrombi occur are surrounded by completely ischaemic tissue, so that the local condition in the artery is probably different from that in minor R.C.N

THIN MURAL THROMBOSIS

This is the type of thrombosis seen in all the distal arterial tree of the centre dead area of gross R.C.N The thrombus consists purely of fibrin, and the total amount is quite small, so that it is not necessary to postulate any considerable amount of blood for its formation. In some cases the operative spasm in the artery has begun as early as 6 hours; in other cases it has been of late development, as is shown by the fact that the first reflow of blood has led to necrosis-changes in the proximal convoluted tubules corresponding to a 9 or 12 hour lesion. The thrombus is seen first at 36 hours, which may be accepted as the time that the spasm finished. It appears therefore that the spasm in the intralobular artery may last for a period of 18 to 30 hours.

When this spasm relaxes, the distal part of the arterial tree has been dead for a long time, and there has been no blood supply in its neighbourhood. When the blood finally enters this distal arterial tree, it spreads rapidly and very evenly throughout it, right out to the glomeruli. The whole arterial tree is immediately dilated The thin mural thrombus is laid down evenly over the entire intima, and forms a plaster thrombus in the dilated stalk afferent vessels. This usually seals the base of the glomerular capillaries, though occasionally some plaster thrombus may reach into these vessels.

The histological appearances of a thin layer of loose fibrin thrombus suggest that the thrombosis occurs very quickly, possibly within a matter of minutes Once the thrombus has formed in the stalk afferent vessels, the reflow of blood must cease.

BASOPHIL INTIMITIS

In some arteries there is a delay in the formation of the thin mural thrombus, possibly because of some peculiarity of the coagulation mechanism. The leucocytes, in the blood which flows into the arteries, become marginated and penetrate the intima. Here they degenerate in precisely the same manner as do the intertubular leucocytes at the inner margin of the polymorph zone. There can be little doubt that this is the manner of production of basophil

intimitis, because the leucocytes are seen in the intima of arteries in the centre dead area far beyond the inward range of the leucocytes in the polymorph zone. After some unknown but probably short period, the degenerating cells in the intima appear to liberate thromboplastic ferments, which lead to the rapid development of thin mural thrombosis and to the arrest of whatever slight circulation is continuing in the artery.

In arteries which are the site of basophil intimitis or of thin mural thrombosis, there is not usually much irruption of red corpuscles or leucocytes into the media. This is presumably dependent on the poor character of the reflow in these arteries.

ABSENCE OF PERIPHERAL THROMBOSIS

In occasional arteries it appears that the arterial spasm is very prolonged and continues until occlusive thrombosis occurs at the site of the operative spasm. As a result, there is no reflow of blood into the distal part of the arterial tree. Thus the dead arteries, though relaxed, are not greatly dilated, and they show no trace of thrombosis or of infiltration of their walls with blood cells. This condition is seen only in occasional cases of gross R.C.N., and in only one of the present series does it appear to have involved all the arteries of the cortex.

SOLID OCCLUSIVE THROMBOSIS OF LARGE ARTERIES

Subsequent to all these changes in cases of gross or patchy R.C.N., there is a sealing-off of the necrosed part of the arterial tree by a homogeneous occlusive thrombus in the trunk of the artery at the lower margin of the area of R.C.N.. This can be accepted as the site of the proximal end of the operative spasm, and the artery at this point has a good oxygen supply in its vicinity. The thrombus is of solid platelet type, and is very similar to the thrombus seen in minor R.C.N.. It is built up by the deposition of platelets and fibrin from the normally circulating blood that washes against the site. It is sometimes formed *de novo*, and sometimes built up on the lower end of a trellis thrombus.

Possibly as a result of the active circulation of blood in the proximal p of this large artery, the thrombus does not appear until about 3 or 4 days. Th it is quite clear that this thrombus is not the cause of the R.C.N. but is mere a late *secondary phenomenon*.

GENERAL ASPECTS OF THROMBOSIS

In much of the early literature, there are long discussions about whethe thrombosis begins at the glomeruli and spreads to involve the arteries, *o versa*. As will be seen from the detailed discussion above, these argu are only of historical interest. Adequate *reference to these papers* found in the reviews by Zalka (1933), Ash (1933), Duff and More and Dunn and Montgomery (1941).

The occurrence of thrombosis in dead vessels may be influenced by a number of factors. When a vessel has just been killed, there is no thrombosis in it during the first hour or perhaps a few hours. Subsequently there is a period of probably a few days, when blood entering the vessel coagulates readily. Finally a stage is reached when blood flowing into the vessel fails to coagulate, as is seen in the inflow of blood into areas of kidney that have been necrosed for more than 2 weeks.

Factors which may delay the formation of the thrombi are (*a*) disturbances of the coagulability of the blood in general during the first day after the U.P.A., (*b*) local production of anticoagulant or fibrinolytic substances by the endothelium of the dead vessels. This latter point is quite theoretical in the present connection, but is raised by the work of Mole (1948) on the development of fibrinolysins in the dead body.

It has sometimes been maintained in the literature that the death of the arterial wall which leads to the thrombosis is due, not to ischaemia as is accepted here, but to toxins. The toxins postulated are of two types: general and local.

The general toxins are variously attributed to "eclamptic toxaemia", to the absorption of substances from retroplacental clot, or to bacterial infections. While it is freely admitted that such general toxins might be responsible for the spasm of the vessels, they do not account satisfactorily for the various types of thrombosis developing many hours after the parenchymal lesions.

The other view is that there is a local formation of toxins in the dead kidney tissue around the artery, and that these toxins diffuse through the arterial wall and damage the endothelium, thus leading to thrombosis. (The ordinary pathological analogy is the thrombosis occurring on the non-ischaemic endocardium over an area of myocardial infarction.) The explanation that the thrombosis of arteries in the renal cortex is secondary to death of the surrounding parenchyma was put forward by Jardine and Kennedy (1913). These authors are among the very few people who have recognised that tubular necrosis does in fact precede the arterial thrombosis. Nevertheless, this theory of local toxins can not be accepted as the explanation of the thrombosis, because there are so many cases of very extensive proximal convoluted tubule necrosis several days old without any trace of thrombus formation in the arteries.

CHARACTER OF THE MARGINAL ZONES

Though the various zones around the centre dead area only begin to be recognisable at 36 to 48 hours, their circulatory basis, and thus their site, is determined during the phase of arterial ischaemia. The re-establishment of the bloodflow to the outer zones may come from two sources:

(*a*) The opening-up of capillary anastomoses from neighbouring areas

in these branches relaxes early enough, there will be a very wide live margin zone in the deep cortex and in the wedges of viable tissue which project out from the juxtamedullary region. A wide live margin zone is in fact sometimes seen in these sites.

There can be little or no blood supply to the peripheral dead zone or the polymorph zone, though there may be some diffusion of fluids into these zones from the zone of partial survival, leading to the development of basophil oedema fluid in the dead tissue.

It has been noted in Chapter VI that, in the outer portion of the partial survival zone, there are sometimes glomeruli whose tufts are sharply divided into a necrosed half facing the centre dead area and a live half facing the normal tissue around. It is not clear how this occurs It is possible that the glomerular capillaries on the side facing the dead area continue in prolonged contraction, as part of the general spasm which affects the whole of this area of R.C.N.

The polymorph zone does not develop until 30 to 36 hours, presumably because leucotaxins are not liberated from the necrosed tissue until this time. There is an initial diffuse migration of leucocytes through the outer zones, with a subsequent concentration entirely in the polymorph zone, which is at a constant distance from the bloodflow in the live margin The remarkably sharp inner margin of this zone appears to indicate a site of critical balance between the oxygen supply from one side and the diffusion of leucotaxic products of necrosis from the other.

There is little or no evidence of the arrival of further polymorphs in this area after about 3 days, as judged by the absence of polymorphs in the outermost zones Furthermore, at about 5 to 7 days all the leucocytes disappear from the area, leaving only the debris of those leucocytes which have perished at the inner surface of the polymorph zone. This suggests that leucotaxins do not diffuse out of the necrosed area after about 3 days, it is not a result of a lack of blood supply, because this would lead merely to the transfer of the polymorph zone into one of the outermost zones The disappearance of the polymorphs is not due to any systemic disturbance, because these patients can produce a good polymorph infiltration around areas of pyelonephritis at any time after the U P.A

REPAIR AND LOCAL REACTION

REPAIR OF TUBULES

The repair of tubular epithelium follows the ordinary course, as is seen in any experimental tubular necrosis. The regeneration has its source in the occasional epithelial cells which remain in the live margin zone, and from surrounding normal nephrons The thin sheet of cytoplasm relines every necrosed tubule where there is a re-established blood supply. The quickness of this repair is a very striking phenomenon.

During the second week, some of the regenerated tubules become separated by new connective tissue, and they soon atrophy and disappear. No real explanation can be offered for this.

ORGANISATION OF OCCLUSIVE THROMBI

The living part of the artery, just proximal to the occlusive thrombus, develops a very rapid endarteritis obliterans at the end of the first week, so that its lumen is occluded by a cellular connective tissue. The organisation of the occlusive thrombus appears to develop mainly from this tissue, and the two processes continue *pari passu*. When finally the whole surrounding region is scarred, the site of the thrombosed artery may be difficult to identify. One indication of the site is given by the sinuses which recanalise the thrombus and the endarteritis.

MEDIAL DEGENERATION

The fibrinoid degeneration of the wall of the thrombosed artery occurs only in the regenerating area where there is some blood supply. The process is not clearly understood, but appears to depend on the attachment of the thrombus to the wall at this site

Greater interest attaches to the fibrinoid change that occurs in non-thrombosed arteries and arterioles of the live margin zone, and sometimes extends up into previously undamaged glomeruli. This lesion shows histological similarities to the fibrinoid necrosis of malignant hypertension. The comparative aetiology of the two lesions will not be discussed here; the point that is relevant in the [illegible] lesion [illegible] that it [illegible] ium is [illegible] raised or not

Some authors, having observed this change in the living tissue around an area of R C.N , interpret it as the early [illegible] arterial lesion which they consider has produced the R.C.N [illegible] ;8; [illegible] in Hunt, 1939; Sheldon and Hertig, 1942, [illegible] or imply that the area of R.C N. is therefore in the process of extending out

into the live surrounding tissue. Such a view cannot be reconciled with the facts that this arterial change does not develop earlier than $5\frac{1}{2}$ days, and that it is not associated with any fresh necrosis of parenchyma. Furthermore, the dead area of R.C.N. never contains any necrotic ghosts of this lesion, as would occur if the necrosis were extending.

PROLIFERATIVE CAPSULITIS

The proliferation of the capsular epithelium in glomeruli in the live margin zone around an area of R.C N. is clearly a local reaction, though it shows remarkable similarities to the capsular proliferation which occurs throughout t[illegible]

F[illegible]

c[illegible]

usually recognised

A few authors, having observed this epithelial crescent formation, and also the repair processes of proximal convoluted tubule necrosis in those parts of the kidney unaffected by the R C.N., have interpreted these changes as indicative of a pre-existent subacute nephritis. This interpretation cannot be accepted, there are never any necrotic ghosts of epithelial crescents or of fibrosed tubules in the dead area of R C.N.. The lesions which these authors reported were clearly only the local repair and reaction-processes which develop around areas of R.C N. several days old

CHAPTER XIII

DISCUSSION OF COGNATE LESIONS

In the present paper the term R.C.N. has been applied only to the particular variety of "infarction" which is apparently due to spasm affecting arteries throughout the cortex, and which is not associated with any other primary local disturbance in the arteries.

In routine autopsy material there are a number of other conditions which are also characterised by multiple ischaemic necroses, either gross or microscopic, throughout the renal cortex. The pathological appearances are in many ways similar to R.C N., and certain of these cases have in fact been recorded in the literature as examples of R.C N.

These other lesions fall into six groups, each of which represents a well defined clinico-pathological entity There is a common factor of multiple ischaemic necroses of the renal cortex in each of these six groups, and also in R.C.N. as defined in this paper. Nevertheless the aetiology of each type is distinctive, and it seems inadvisable to extend the term R.C.N. to cover all these conditions.

MALIGNANT HYPERTENSION

Quite commonly in cases of malignant hypertension there are small foci of ischaemic necrosis in the cortex, varying from lesions of a single glomerulus up to those which involve several glomeruli and the associated parenchyma Occasionally the condition is so severe that it could be considered macroscopically to be a minor or even a patchy R.C.N.. In cases where one kidney is "protected" from the malignant hypertension by gross arteriosclerotic narrowing of the renal artery, the ischaemic necroses are seen only in the other kidney, and such cases have been recorded as unilateral R.C.N. (Aronson and Sampson, 1951).

... be histologically

...re are commonly

... of parenchyma,

which are indicative of a more gradual development ot ischaemia The histological appearances of the arteries in malignant hypertension are usually characteristic. Nevertheless they seem to be basically related to those seen in focal and confluent R.C.N., this suggests that there may be similarities in their aetiology. The local disturbance in malignant hypertension is presumably some combination of vascular spasm and fibrinoid necrosis of the arterial wall in the presence of a high blood pressure; lesions of this general type have been

produced experimentally by pituitrin (Byrom, 1937), adrenalin (Penner and Bernheim, 1940), and *increased intravascular tension* (*Byrom and Dodson*, 1948). The case of R.C.N. recorded by Haft and Prior (1951) may have resulted from the intracardiac injection of adrenalin.

PERIARTERITIS NODOSA

In certain cases of periarteritis nodosa there are multiple areas of ischaemic

[illegible]

not be confused with the cellular infiltration which may occur in the necrosed arterial wall at the polymorph zone in gross or patchy R.C.N.

SCLERODERMA

In a certain proportion of cases of scleroderma the larger intralobular arteries become dilated and develop peculiar mucoid thickening of the intima. This produces ischaemic atrophy of the related parts of the cortex. After a few weeks a fibrinoid necrosis occurs in the smaller intralobular arteries, and produces multiple areas of ischaemic necrosis in the outer part of the cortex. The patient dies within a few days. At autopsy the kidney has the appearance of a focal or minor R.C.N.. This subject has recently been reviewed (Moore and Sheehan, 1952); other cases not reviewed in that paper have been reported by Duffy and Bardsley (1951), Lunseth, Baker and Shifrin (1951), and Sharnoff, Carideo and Stein (1951).

OTHER COLLAGENOSES

These other conditions which may give rise to small areas of ischaemic necrosis in the kidney include the diseases in which some form of involvement of visceral arteries is a common complication: disseminated lupus erythematosus, dermatomyositis, thromboangiitis obliterans, etc. Recent references are given by Yardumian and Kleinerman (1949) and by Bradley, Drake and Mack (1951).

EMBOLIC INFARCTION

Certain embolic infarcts seem to be due to the complete mechanical occlusion of a large branch of the renal artery or of an interlobar artery which has no adequate anastomoses. In such a case, massive infarction occurs in the cortex and medulla, and there is no reflow of blood into the area. Similarly, the total obstruction of a single intralobular artery by an embolus will produce a narrow column of necrosis in the cortex; the intralobular arteries are essentially end-arteries.

The common infarcts in the kidney appear however to be produced in a rather different manner. Characteristically the infarct is about 5 to 20 mm. in diameter. It is mainly limited to the cortex, and frequently to the outer three-quarters of the cortex. In some places it extends down to involve the juxtamedullary nephrons and, at this site, there may be a relatively small tongue of necrosis running down into the medulla.

The only satisfactory explanation for a wide infarction of the cortex not involving the medulla and deep cortex is that some disturbance (such as the impaction of an embolus) has occurred in the related interlobar or arcuate artery, but has not produced a complete arrest of the circulation through it. The continuance of at any rate some blood flow may be because the embolus has led to only a partial occlusion, or because there are anastomoses from other arteries. There are two possible reasons for the infarction of most of the cortex in the area Either (*a*) the continuing bloodflow, whether direct or anastomotic, is only sufficient to nourish the deeper layers of the cortex and the medulla, and is inadequate to supply the remainder of the cortex, or (*b*) the mechanical irritation of the embolus in the interlobar artery may lead to a reflex spasm in all of its intralobular branches a little distance above their origins, as has been discussed in the section "*Aetiology of the spasm*" in Chapter XI. Clearly these two explanations are quite compatible with one another, and both factors may well operate to produce the infarction. There is no direct evidence on the matter, but histological examination of the infarct usually shows some indication of a period of reflow of blood, so that the microscopic [illegible] In fact, [illegible] ietimes [illegible] Burne, 1951). In view of the different aetiology, the two conditions should be kept separate.

VENOUS THROMBOSIS IN CHILDREN

In small children a haemorrhagic infarction of the kidney may occur, involving sometimes the whole organ and sometimes only a part. Associated with this, renal veins of various sizes are usually thrombosed, though it may be difficult to relate the site of the thrombosis to the site of the haemorrhagic infarction (Mallory, 1949; McClelland and Hughes, 1950; Kobernick, Moore and Wiglesworth, 1951; Zuelzer et al, 1951). These cases form a distinctive group and will not be considered further in this paper.

CHAPTER XIV

CLINICAL CONDITION DURING THE PUERPERIUM

The relation of the pathological lesions to the clinical aspects remains to be considered:

(1) The incidence of the various renal lesions following U P.A.
(2) The clinical differentiation of these lesions.
(3) The functional effects of the renal damage
(4) The possible lines of treatment

THE INCIDENCE OF RENAL LESIONS FOLLOWING U P A.

It is possible to give only very uncertain estimates of the actual incidence of the various renal lesions among all cases of U P.A , i.e. including the non-fatal as well as the fatal cases.

The present series of fatal cases may be divided into those where death occurred during the first day, mainly as a result of shock and haemorrhage or hypertensive toxaemia, and those where death occurred later in the puerperium, either as a result of severe renal insufficiency or of incidental causes. The cases can also be classified into four grades according to the degree of renal insufficiency. In the cases which survived several days, this degree is that which actually occurred. In the cases which died in the first day, the degree is that which, from histological assessment, would have developed if the patient had survived long enough T[illegible] fatal, (*b*) severe lesions carryi[illegible] slight lesions which are repai[illegible]atients should recover, (*d*) no significant renal lesions, so that any puerperal deaths would be from other causes

The combined classification is shown in Table 6.

TABLE 6 *Renal lesions in fatal cases*

Renal lesions	Deaths during *first day*	Deaths later in *puerperium*
(*a*) Gross or patchy R C N	4	18
(*b*) Minor or focal R C.N , or extensive tubular necrosis.	9	8
(*c*) Minor tubular necrosis, colloid degeneration and proteinuria lesions .	18	3
(*d*) No renal lesions	5	2

The 67 fatal cases may be taken as coming from 626 total cases of U.P.A., calculating from the overall mortality rate of 10.7 per cent, as discussed in the section on maternal mortality in Chapter II.

The 22 cases of gross or patchy R.C.N. (grade *a*) can be accepted as the full incidence of this condition, since it is most unlikely that any of the patients would survive. It will be noted that one-fifth of these patients died of shock and haemorrhage during the first day.

The 17 cases of less extensive R.C.N. or severe tubular lesions (grade *b*) include 9 deaths during the first day. Assuming that the proportion of cases dying of shock and haemorrhage during the first day was as high in this grade as in the previous one, these 9 early deaths would represent a total of 50 cases in this grade. Thus out of the estimated 41 patients who survived the first day, only 8 died later in the puerperium. On pathological grounds these figures seem not unreasonable

The 21 cases of easily repairable kidney lesions (grade *c*) include 18 deaths during the first day and, quite understandably, only 3 later deaths. If it were to be provisionally considered that these patients had suffered from shock, haemorrhage and toxaemia of the same degree of intensity as in the previous two grades, the 18 early deaths would represent a total of 99 cases of U.P.A with this degree of renal damage. But it is certainly probable that the U.P.A. which leads to these slighter degrees of renal damage is clinically of a less serious type, and thus produces a correspondingly lower incidence of fatality during the first day If this be so, the figure of 99 must be increased, possibly very greatly.

The 7 cases without renal lesions (grade *d*) include 5 deaths during the first day. On the hypothesis that, irrespective of the grade of kidney damage, all the patients have the same liability to death during the first day, these 5 early deaths would correspond to only 29 total cases of U.P.A.. This hypothesis is obviously not acceptable There must be very many cases of U.P.A. which are too slight either to damage the kidney or to produce death during the first day. The allowance for these cases would involve a very considerable increase in the provisional figure of 29

It will be clear that the basic estimated figures account for only 200 cases of U.P.A. instead of 626 The 426 patients who recovered, but are not accounted for, can be distributed among the last two grades, either in the same proportion as the deaths during the first day (i.e. 333 and 93), or almost all to the last grade, or, probably more fairly, divided evenly between the two grades.

These very approximate calculations can be summarised as follows:

(*a*) About 3.5 per cent of all patients with U.P.A develop gross or patchy R.C.N. and will almost inevitably die.

(*b*) About 8 per cent develop a less severe grade of R.C.N., or have extensive tubular necrosis. It is possible that about two-thirds of these may recover.

(c) An unknown number, somewhere between 16 and 70 per cent, have minor renal lesions carrying only a low mortality from renal insufficiency during the puerperium. Tennent and Starritt (1951), in a clinical study of 17 cases of U.P.A., observed some degree of renal insufficiency in the puerperium in 8 of them. This suggests that the incidence of the minor renal lesions is about 35 per cent.

(d) The remainder, probably about half of the cases, have merely a transient albuminuria.

CLINICAL CLASSIFICATION BY URINE OUTPUT

Of the various methods of clinical assessment of the overall damage to the kidney, the most useful is the observation of the volume of urine excreted each [illegible] al insufficiency [illegible] he cases in the [illegible] 16 cases in the literature and 2 personally studied cases where the patients recovered after evidence of severe renal failure following U P A . Some of these recovery-cases were probably examples of focal or minor R.C N ; they had haematuria for the first two or three days after the U.P A . The others may have had merely a severe proximal convoluted tubule necrosis; the diagnosis can only be speculative

The patients may be divided into seven clinical groups according to the following criteria:

(a) 29 cases. Total or almost total anuria, with a urine output never over 50 cc per day These cases were all fatal, the average duration of life being 7 days after the U P.A . Some lived for 11 days, and occasional cases even a few days more

(b) 13 cases. Continued very severe oliguria, with a daily urine output never exceeding 100 cc during the first 7 days These cases were all fatal, the average duration of life being 8 days after the U P A

(c) 5 cases Considerable oliguria for the first 3 days, followed in the next 2 or 3 days by almost complete anuria These cases were all fatal, the average duration of life being 9 days after the U P A. It is difficult to explain the delayed urinary supression in this peculiar group.

(d) 14 cases. An initial severe oliguria, with slight improvement after the 4th day. Some of the patients had a daily urine output up to 500 cc by the 7th day, and even more in the next day or two, but there was no gross diuresis subsequently This group is composed only of fatal cases, the average duration of life being 8 days after the U.P A

(e) 10 cases An initial severe oliguria, or sometimes complete anuria, for about 4 days. The daily urine output was sometimes up to 500 cc by the 7th day, was about 1 to 2 litres at 10 days, and subsequently rose to 4 or 5 litres in

occasional cases. This group consists only of the patients who recovered. This group and the previous one are so similar in their renal function that they may reasonably be regarded as the recovery-cases and the fatal cases of one larger single group

(*f*) 4 cases. An initial severe oliguria, with rapid improvement from about 4 days onwards. All these patients passed more then 500 cc. of urine per day by the 7th day, and some had an output exceeding 1500 cc. Subsequently the urine output increased considerably. This group includes only the fatal cases of this type, with an average duration of life of 11 days.

(*g*) 8 cases. An initial severe oliguria, with rapid improvement from 4 days onwards, so that by the 7th day the urine output was usually over 1500 cc. per day and by the 10th day was occasionally 5 litres. This group is made up only of patients who recovered. The clinical course is almost the same as in group *f*; the only real difference is that the cases in that group were fatal, whereas the cases in group *g* survived.

In addition there are of course large numbers of cases of U.P.A. followed by only minor transient renal insufficiency; such cases are not analysed here.

In this section, certain average figures of urine output and blood chemistry are given in tabular form. These mean figures are calculated only for the purpose of giving a broad picture of the clinical course in each group. The calculations can not be claimed as of any statistical significance. Some of the groups contain only small numbers of cases; other groups gradually diminish as a result of deaths, so that after 7 days there are only a few remaining cases to form the basis of calculations. There are considerable variations between different cases in any group. In some cases there are no data for a particular day, and figures have had to be interpolated from the data on previous and subsequent days. Nevertheless it is believed that the calculations are sufficiently reliable for general deductions, and give reasonable approximation to the truth.

DETAILS OF URINE OUTPUT

The mean output of urine on each day after the U.P.A. is given for each group in Table 7. The output gives a rough indication of the prognosis, at a time in the puerperium when the concentrating power of the kidneys is very low. The prognosis given here is based on conditions before the modern treatment of the anuric patient was introduced.

Little importance can be attached to the urine volume on the first day. Most patients who have U.P.A develop an immediate oliguria, which may clear up in a few hours if the kidneys are undamaged, but which may continue [illegible]

urine secreted before the onset of the U.P.A.

The degree of oliguria from the second to the fourth day is not a reliable guide to the prognosis, though an output of over 150 cc. on the third day and of over 250 cc on the fourth day certainly gives grounds for optimism.

The development of a better urine output, of 500 cc or more, on the fifth or sixth days is even more encouraging By the seventh day it is possible to make a rough assessment of the outlook. If the urine output on that day is below 200 or 300 cc. the outlook is almost hopeless. If it is in the region of 500 cc. there is probably a moderate amount of kidney tissue, either healthy or in process of active repair; many of these patients will die, but a few will develop a considerable diuresis during the second week, and will recover If the urine output on the seventh day is in the region of 1000 or 1500 cc there will certainly be a gross diuresis during the second week, and most of the patients will recover Nevertheless even with this good output there is still danger of death during the second week, though modern treatment should reduce the mortality

TABLE 7 *Mean urine output; cc. per day*

Clinical group	Day after U.P.A.										
	1	2	3	4	5	6	7	8	9	10	11
a	21	9	4	4	5	5	8	19	20	10	13
b	135	60	55	59	30	56	73	80	75	63	70
c	164	408	308	210	108	3	18	20	30	—	—
d	62	53	68	111	153	271	220	300	320	410	375
e	31	27	17	37	84	166	300	570	910	1500	2030
f	81	95	274	410	690	670	940	1610	2110	plus	plus
g	30	115	130	220	290	620	1500	2100	2900	plus	plus

RELATION OF URINE OUTPUT TO RENAL PATHOLOGY

Table 8 shows that most of the patients in clinical groups *a*, *b*, and *c* have gross or patchy R.C.N There are a few patients with only minor or focal R.C.N.; in these cases the poor urine output suggests that the remainder of the kidney tissue was severely damaged by proximal convoluted tubule necrosis or by cast obstruction Both these conditions can give rise to anuria. It is possible that group *c* develop their delayed anuria as a result of the late formation of casts, but this explanation is only tentative.

Group *d* has a few cases of severe R.C.N.; presumably in these cases the remaining kidney tissue must have been relatively healthy and capable of fairly good function There are a larger number of examples of focal R.C.N. and of purely tubular lesions, such as proximal convoluted tubule necrosis or cast obstruction. There is no information about the kidney pathology in the related series of recoveries, group *e*, but it seems reasonable to assume that they were mainly cases of focal or minor R.C.N. or of severe tubular lesions

Group *f* had only focal R.C.N. or severe tubular lesions. One patient in the corresponding recovery series, group *g*, had a biopsy and showed a focal R.C.N. (Crook, 1926).

TABLE 8. *Number of cases with each renal lesion at autopsy, grouped according to urine output*

Clinical group	Severity of R C.N.				Purely tubular lesions
	Gross	Patchy	Minor	Focal	
a	15	11	2	1	0
b	3	8	2	0	0
c	3	2	0	0	0
d	3	3	0	3	5
e	—	—	—	—	—
f	0	0	0	2	2
g	—	—	—	1	—

OTHER CLINICAL PATHOLOGY

URINE UREA

During the first few days of a severe renal lesion, any urine which is formed is extremely dilute. Its urea content gradually increases The estimation of the urine urea requires specific biochemical methods, as the urine may have a high ammonia content, corresponding to a urine urea of 50 to 90 mg. per 100 cc. When this is allowed for, the urine urea in a severe case may be at precisely the same figure as the blood urea for the first few days; in other words, the urine is quite unconcentrated glomerular filtrate.

Towards the end of the first week, the urine urea is usually about 300 to 700 mg per 100 cc. At this time the cases divide into two broad types: (*a*) Those whose urine urea does not rise appreciably above the blood urea, the concentration factor being about 1.0 to 1.4; these patients usually die within the next few days; (*b*) Patients whose concentrating power gradually improves, so that the urine urea is about twice the blood urea at 7 days These patients usually continue improving, so that at 14 days the urine urea is 700 to 1000 mg. per 100 cc. and the concentration factor is 3 0 or more. At 3 weeks the urine urea is about 1000 mg. per 100 cc , but the blood urea has fallen to about 50 mg. per 100 cc., so that the concentration factor is about 20. Nearly all these patients eventually recover

There are not many data about urine urea levels, so that this subdivision of cases can at present only be tentative. This aspect requires further study before its value in prognosis can be determined.

URINE CYTOLOGY

The first urine which is passed after the U.P A , by patients who are developing R.C.N., is usually very heavily blood-stained, and may consist of almost pure blood. The haematuria usually becomes considerably less after the first day, though it may continue for several days It seems probable that this blood comes either from the congested zone at the edge of large areas of early R C N., or from small areas which represent early focal R.C.N.. On general pathological grounds it appears unlikely that purely tubular lesions would give rise to haematuria, though it is not impossible that in these cases some transient bleeding might occur from glomeruli which have been slightly damaged Haemorrhage from obstetric lesions of the bladder must, of course, be excluded.

Investigations of the urine during the first day are difficult because of the shocked condition of the patients, the obstetric complications, and the very small amounts of urine which are produced. Nevertheless there is certainly a need for study of the urine during the first day or two, with regard to the exact time of its appearance in the bladder and in its relation to the particular pathological lesions in the kidney Some information is available in one fatal case of patchy R.C N in the present series: Case 51 An indwelling catheter was left in the bladder, and accurate observations were made of the urine output There was no urine up to 24 hours In the next 2 hours, 7 cc of blood-stained urine was obtained. Following this, no urine was obtained up to 44 hours. In the next 12 hours, 1 cc of blood-stained urine was produced each 3 hours, and 5 cc. in the next 2 hours. For the last 8 hours there was again complete anuria

Nearly all of these patients with oliguria have some degree of pyuria after the first day, and this may become considerable and continue for a week or two There are three possible causes: (*a*) The development of the polymorph zone around areas of R.C.N. will allow leucocytes to escape into the urine (*b*) Most of these patients are catheterised frequently or have a self-retaining catheter, so that cystitis may occur. (*c*) As a result of the lower urinary tract infection associated with the severe oliguria, a suppurative pyelonephritis develops not uncommonly near the end of the first week It is thus very dangerous to draw conclusions about the existence of R C N from the presence of polymorphs in the urine

Despite the formation of casts in the intermediate zone or the collecting tubules in the kidney, there are usually very few or no casts in the urine It is possible that some casts are washed out during the period of diuresis, and are not recognised at that stage

PROTEIN CONTENT OF THE URINE

The first sample of urine obtained very soon after the U P A. may consist mainly or entirely of urine which was already in the bladder at the time

Group *f* had only focal R.C.N. or severe tubular lesions. One patient in the corresponding recovery series, group *g*, had a biopsy and showed a focal R.C.N. (Crook, 1926).

TABLE 8. *Number of cases with each renal lesion at autopsy, grouped according to urine output*

Clinical group	Severity of R.C.N.				Purely tubular lesions
	Gross	Patchy	Minor	Focal	
a	15	11	2	1	0
b	3	8	2	0	0
c	3	2	0	0	0
d	3	3	0	3	5
e	—	—	—	—	—
f	0	0	0	2	2
g	—	—	—	1	—

OTHER CLINICAL PATHOLOGY

URINE UREA

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the blood urea shows only a slight rise, but these cases do not come within the province of the present analysis.

Table 10 shows the mean blood levels of creatinine, uric acid, and total non-protein-nitrogen There are insufficient data to classify the mean figures in relation to the clinical groups, but an examination of the actual case records shows no apparent difference between the various groups The creatinine remains rather low in a few cases. The uric acid appears to be raised at the time of, or very soon after, the U.P.A ; the mean level in 5 cases at 12 hours was 6 7 mg. per 100 cc.

TABLE 10 *Other blood chemistry mg per 100 cc*

All groups	Day			
	1	4	7	10
Creatinine	2 6	6 7	7.9	12 7
Uric acid.	7.4	9 4	12 3	15 0
Total N.P N. . . .	43	115	181	220

It might be expected that there would be a steady continuous rise of the various N P.N. substances in the blood in any individual case where little or no urine was being secreted. In fact the rate of rise may show peculiar minor fluctuations from one day to the next, and on some days there may even be a slight fall. The fluctuations of any one of the substances appear to be unrelated to the fluctuations of the others They are not related to any large excretion of [illegible] lays. They have been observed in several [illegible] al errors have, as far as possible, been [illegible] They may possibly depend on the diet, or on vomiting or diarrhoea. Whatever their explanation, these fluctuations have no prognostic significance, though a steady and continued fall is of course of good import.

The act [illegible] N P N [illegible] depends on various factc [illegible] is o [illegible] treatment Endogenous nitrogen comes from two sources· (1) from involution of the uterus, and from absorption of blood in the haemorrhages in the uterus and appendages (2) [illegible] which may be high if the patier [illegible] an adeq [illegible] nay produce, from tissue breakdown, 8 or 10 gm of urea per day, whereas a patient whose tissues are spared by an adequate fat and carbohydrate diet may produce as little as 2 5 gm. of urea per day

The number of variable factors is obviously so great that it is not surprising that the blood urea shows no significant differences between the clinical groups

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TABLE 10. *Other blood chemistry: mg. per 100 cc.*

All groups	Day 1	Day 4	Day 7	Day 10
Creatinine .	2.6	6.7	7.9	12.7
Uric acid.	7.4	9.4	12.3	15.0
Total N.P.N. .	43	115	181	220

It might be expected that there would be a steady continuous rise of the various N.P.N. substances in the blood in any individual case where little or no urine was being secreted. In fact the rate of rise may show peculiar minor fluctuations from one day to the next, and on some days there may even be a slight fall. The fluctuations of any one of the substances appear to be unrelated to the fluctuations of the others. They are not related to any large excretion of urine during the first 10 days. They have been observed in several cases personally studied, and technical errors have, as far as possible, been avoided by duplication of estimations. They may possibly depend on the diet, or on vomiting or diarrhoea. Whatever their explanation, these fluctuations have no prognostic significance, though a steady and continued fall is of course of good import.

The actual rate of rise of these various N.P.N. substances depends on various factors. Exogenous nitrogen from food may vary from day to day if the patient is on a mixed diet, as was the case before the introduction of the modern treatm[illegible]
of the [illegible]
and ap[illegible]
patient [illegible]
adequate diet of fat and carbohydrates. For example, a starving pat[illegible]
produce, from tissue breakdown, 8 [illegible]
whose tissues are spared by an [illegible]
produce as little as 2.5 gm. of urea per day.

The number of variable factors is obviously so great that it is not surprising that the blood urea shows no significant differences between the clinical groups.

In general, the blood urea does not reach the high levels which are seen in lower nephron nephrosis (Humphrey and Jones, 1948); this may be of value in the differential diagnosis. The further investigation of this problem would require very complex biochemical balance studies.

HAEMATOLOGY

There is always some anaemia in the early stages after a U.P.A.. The blood of the normal patients, in the hospital where most of these cases were observed, has a mean haematocrit reading of 38 per cent at the time of delivery; this falls to about 33 per cent from the second to the sixth day of the puerperium, and then gradually rises to about 42 per cent in the course of the next few weeks (Crawford, 1940).

After a patient has had a moderate U.P.A., the mean haematocrit reading is about 29 per cent; following the delivery this falls to about 20 per cent, and stays at this level for a few days.

The patient who has had a severe U.P.A. has a haematocrit reading of about 19 per cent before delivery; at this time her serum is yellow and gives an indirect van den Bergh reaction, with a bilirubin content of about 2 mg. per 100 cc. After the delivery the haematocrit reading falls to about 12 per cent, and the serum bilirubin rises to about 3 mg. per 100 cc. During the next two days the excess bilirubin gradually disappears from the serum, but the haematocrit reading stays at about 12 per cent. It is difficult to ascertain the subsequent course of the haematocrit reading, because many of these patients are given blood transfusions during the puerperium. From the few data on patients who did not have a transfusion, it appears that some of the patients improve gradually to a haematocrit reading of about 20 per cent at about 2 weeks, whereas others show no improvement during the first two weeks, and may even fall below the level of 12 per cent.

There is insufficient information to determine how often the U.P.A is [illegible]

seen in these cases (Sheehan and Falkiner, 1948). The fall at the time of the U.P.A is certainly related to blood loss; many of these patients have retroplacental clot weighing 500 to 1000 gm. or more, and there is sometimes external haemorrhage in addition. The transient bilirubinaemia is presumably due to the absorption of blood pigments from the uterus. The fall in the haematocrit reading after delivery, and its subsequent low level, is an exaggeration of the usual puerperal fall, probably as a result of the preceding oedema and the general illness, as pointed out by Crawford (1940). In the few cases in which blood volumes have been measured, figures of about 4 litres are recorded both before delivery and during the puerperium.

Patients who have renal impairment in the puerperium are usually very anaemic at that time, presumably as a result of the severity of the U.P.A.. Apart from this, there is no obvious relation between the blood count and the renal pathology.

The leucocyte count in the first 2 or 3 days of R.C N is raised to the level which normally occurs at this stage in the puerperium, with counts of 14,000 to 18,000 per cu.mm. (Henderson, 1902) From the 4th to the 7th day, the white count continues elevated to about the same level instead of showing the normal fall, and occasional cases may have counts of over 20,000 per cu.mm. After this time the figures are complicated by the frequency of suppurative pyelonephritis, which in some cases may produce a leucocytosis of 20,000 to 40,000 per cu.mm. There is no available evidence as to the counts in cases of pure proximal convoluted tubule necrosis.

It does not appear that these blood examinations are of any particular value in assessing the prognosis.

BLOOD COAGULATION

Evidence has recently been produced that the *in vitro* coagulability of blood from the general circulation is lowered or abolished in some cases of U.P.A (Dieckmann, 1936; Dam, Larsen and Plum, 1941; Dieckmann, 1942; Weiner, Reid and Roby, 1950; Schn
just as it is in certain cases c
to 6 hours after the U P.A.
level and may actually disappear, the blood prothrombin falls more slowly but may be about a third of its normal level at about 8 or 9 hours A fibrinolysin may be present for a short period at about 4 to 6 hours The fibrinogen and prothrombin return to normal after about 24 to 36 hours.

These *in vitro* abnormalities may be associated with clinical evidence of disturbances of coagulation, such as the occasional development of severe post-partum haemorrhage and the great difficulty sometimes found in controlling oozing of blood after Caesarean section or hysterectomy The occurrence of retroplacental clot in these cases presents no problem; this clot has already formed before the gross disturbance of the coagulating mechanism The possible influence of these factors on the rate of thrombosis in the arterial tree of the kidney has been mentioned earlier

CLINICAL COURSE

The clinical course of the illness is practically the same in patients with any grade of R C N as in those with only a severe proximal convoluted tubule necrosis The former have haematuria and subsequent pyuria, and may have a lower output of urine; otherwise there is little to differentiate the conditions.

The patients usually seem remarkably well, are mentally clear, and have a moderate appetite, though they may have troublesome vomiting or hiccough. There may be a transient pyrexia on the third day (MacGillivray, 1951) but otherwise the temperature and pulse rate remain normal in the absence of complications.

Blood pressure. It has been pointed out earlier that the blood pressure is usually well maintained during the shock which accompanies the U.P.A. Subsequently most of the patients have a moderate hypertension, though the systolic blood pressure may fluctuate 30 to 50 mm. from day to day.

Table 11 shows the mean figures for about 40 cases; there is no obvious difference between the different pathological groups.

TABLE 11. *Blood pressures during puerperium*

Day	Blood pressure: mg. Hg. *Mean*	*Range*
During U.P.A.	137/88	230/130 to 90/60
1	158/100	210/140 to 135/90
2	150/91	200/120 to 110/75
3	150/90	210/140 to 105/60
4	153/95	200/140 to 130/70
5	160/90	220/125 to 115/75
6	150/91	200/120 to 110/60
7	157/90	200/120 to 130/80
8	166/95	185/130 to 130/80
9	153/92	190/120 to 120/80
10	140/100	160/115 to 110/80
11	145/105	150/110 to 140/100
12	160/115	160/120 to 160/110

It will be seen that the mean blood pressure remains relatively constant. By the 9th day very many of the patients have died, so that there are few data after that time in the protocols. As a result, the subsequent figures are less reliable; in particular the validity of the late rise of the diastolic pressure is uncertain

MANNER OF DEATH

After a few days there may be attacks of dizziness or muzziness which last a few hours, and which very occasionally are accompanied by convulsions.

At some time, usually between the 5th and 10th day but occasionally later, the patient has one or two sudden episodes of a peculiar and very severe

collapse. She becomes cold and clammy, the pulse is very weak, and she appears moribund. She may die quickly in the first attack, or may make a dramatic recovery within an hour or two. In the latter case, a second attack usually follows during the next day, and she succumbs during it. This manner of death is precisely the same in patients with proximal convoluted tubule necrosis as with any grade of R C.N.

The cause of the sudden collapse and death in these cases appears to be probably a cardiac irregularity due to hyperpotassaemia, similar to the cause of the sudden collapse which occurs in other acute anurias, such as the crush syndrome or the transfusion kidney.

The plasma electrolytes were studied in only two of our own cases and in only 5 of the fatal cases reported in the literature, but there have been several recent reports of clinical cases of presumed R.C.N in which the subject was investigated in detail. The plasma potassium may be within normal limits until a day before death, when it rises to 25 or 30 mg. per 100 cc ; in other cases it may be high from the start (29 to 33 mg. per 100 cc.) The factors which *may* give rise to a high potassium are breakdown of tissue cells, haemolysis in the body, convulsions at about the time of delivery, the administration of potassium citrate or fruit juice, and hypertonic intravenous therapy. The toxicity of the potassium is enhanced, among other things, by a low level of the plasma sodium The clinical diagnosis of significant hyperpotassaemia is best made by a careful study of the electrocardiogram; this subject is excellently reviewed by Merrill et al. (1950)

The plasma sodium is usually at low normal levels or slightly reduced (280 to 300 mg per 100 cc), possibly as a result of vomiting The serum calcium is usually at low levels (7 2 to 8 8 mg per 100 cc) possibly in relation to the high

gradually, levels of 15, 27, 29, 38 and 40 volumes of CO_2 have been recorded. It is of interest that the fall of alkali reserve is not accompanied by air hunger.

EARLY TREATMENT

If the proximal convoluted tubules are to be saved, the time at which the spasm in the arterial tree must be relaxed is within about 2 to 3 hours after the U.P.A . If the grosser lesions are to be obviated, the spasm must be relaxed within about 6 to 8 hours At this early stage the clinical condition of the patient is usually poor, there is as yet no clinical evidence of serious renal damage; and there is a good prospect that the spasm in the cortical vessels will relax spontaneously, as it does in the majority of patients By the time the renal lesion is clinically manifest, the time for active measures to relieve the spasm has passed.

On the assumption that the cortical vascular spasm is a result of the uterine disturbance, there is a *prima facie* case for rapid delivery. Many of the patients are in labour at the time of admission, and are usually delivered quickly and easily if the foetus is small. On the other hand when the patient is not in labour, or when she has a large foetus so that the labour may take many hours, Caesarean section should be considered. With adequate transfusion and the use of antibiotics, this operation in cases of U.P.A. appears to have a much lower mortality than it had twenty years ago (Hollenbeck and Williams, 1951). The purpose of immediate section, in the present context, is that it might prevent the continuance of the arterial spasm in the kidney, but the assessment of any such effect presents some difficulties The transfusion and section could possibly save patients who had already suffered severe renal damage and who would ordinarily die of shock and haemorrhage during the first day. This might reveal more clinically recognisable cases of R.C.N. in the puerperium.

Blood transfusion itself is of definite value in preventing early deaths from U.P.A (Sheehan, 1942). However, there is no reason to suppose that it would have any significant effect in preventing the renal lesions. The cause of the cortical ischaemia is vascular spasm, not blood loss.

There is as yet no information about the efficacy of direct attempts to relieve the cortical vascular spasm at this particular time in human patients. Renal splanchnic block has been employed by various methods: surgical attack on the splanchnic nerves or the renal plexus, high spinal or local anaesthetics, or medical treatment by drugs of the tetraethylammonium bromide group. The difficulty in assessing the value of such treatments is that they are usually not begun until after the renal lesions have developed. Tetraethylammonium bromide may in fact decrease renal bloodflow (Aas and Blegen, 1949)

Patients with U P.A. sometimes have very severe post-partum haemorrhage, for which pituitrin or ergot may be prescribed. On theoretical grounds it seems prudent not to use these drugs because of their possible vasoconstrictor effects on the kidney. There have however been no studies of their actual influence on the incidence of renal damage following U.P.A

One further purpose of early treatment is to try to prevent the formation of casts, and in particular of proteinuria casts in the collecting tubules of those nephrons which have remained relatively undamaged. This might be achieved by producing a maximum flow of dilute urine through these tubules during the period from about 8 to 24 hours. The production of such a diuresis is intimately bound up with the treatment of the renal vasoconstriction. The intravenous administration of glucose-saline might possibly be of some value during this particular period, in 'flushing' the tubules if the kidney is able to excrete the fluid. On the other hand many of the patients have some degree of oedema and presumably have a sufficient 'head of fluid' in the tissues, so that intravenous glucose-saline is not indicated. The problem of preventing the

formation of colloid casts in the intermediate zone in the period between 3 and 12 hours after the U.P.A is a more complex one, though it is possible that the administration of fluids might be of some use.

The administration of alkalis during the early stage has as its purpose the prevention of acidity of the urine, a condition which is requisite to the precipitation of protein as casts in the tubule (Baker and Dodds, 1925). Such therapy has a rational place only during the first day after the U.P.A.. Modern views on this subject have been reviewed by van Slyke (1948).

LATER TREATMENT AND RECOVERY

The question of the recovery of patients with R.C.N has been discussed by Gibberd (1936) and by several subsequent workers. Acceptable cases have been recorded by McKerron (1902, Case 1), [illegible]
(1926), Kellog et al (1928), Krellenstein (19[illegible]
2), Groen and Lindeboom (1940, Cases 1 [illegible]
O'Sullivan and Spitzer (1946, Case 5), Gra[illegible]
Durrans (1949), Mauzy and Donnelly (1949, Cases 2, 3 and 4), Bergqvist (1950, Cases 1 and 2), Merrill et al. (1950, Case 2), Bull, Joekes and Lowe (1950, Case 82563), Priddle and Stevenson (1951, Case S M)

The extent of the R C.N is only of indirect importance in the resumption of renal function The significant factor is the amount and condition of the remaining parts of the cortex The patient with gross or patchy R.C.N has usually a considerable degree of proximal convoluted tubule necrosis in the remaining cortex, and, even if that tissue were quite healthy, the amount remaining is so small that the patient must almost inevitably die The patient with minor or focal R C N also has much necrosis of proximal convoluted tubules, but there may be a fair number of nephrons remaining relatively intact. If the patient can be kept alive by these nephrons for a week or two, until the necrosed tubules have regenerated and resumed function, she may survive. The patient with extensive proximal convoluted tubule necrosis has similar prospects to the patient with the lesser degrees of R C N . The case reported by Crook (1926) proves conclusively that a patient with focal R.C.N. can recover.

Clearly the recovery of the kidney is, to a very large extent, a question of the recovery of tubules. The sequence of events in a single nephron with a necrosed proximal convoluted tubule is as follows There is an initial period of about 3 to 5 days when any glomerular filtrate escapes directly through the denuded basement membrane of the tubule and returns to the blood stream The nephron as a whole is therefore anuric. The second stage occurs when the tubule is relined by low basophil epithelium. This epithelium can function as a duct to carry glomerular filtrate along the lumen, but it is unable to concentrate the filtrate or to perform selective reabsorption or secretion The nephron at this stage passes a large amount of fluid which is unelaborated

glomerular filtrate. In the course of the next few days, the regenerated epithelium develops more normal histological appearances and gradually takes on its normal functions. The urine from the nephron slowly becomes more concentrated, and there is now selective reabsorption and secretion. In the course of about 3 weeks the nephron has returned to almost full function.

Though there may be a difference of perhaps a couple of days between the repair stages of different nephrons, the secretion of urine by the kidney as a whole represents the sum of the return of function of all the repairing nephrons. Thus, during the first few days, the patient may pass no urine at all or may pass a little very dilute urine from those nephrons which have remained almost undamaged Following this, there is a period of a week or two when the patient has gross diuresis with a steadily increasing concentration of the urine. In the early part of this diuresis phase, sodium and chloride may be lost in large quantities, but the power to retain these ions gradually returns in the later stages. Finally there is a period of a few months in which there is no obvious renal insufficiency but renal function tests disclose some inadequacy.

In the case of nephrons where there has been formation of colloid casts in the intermediate zone, or proteinuria casts in the distal convoluted or the collecting tubules, a period of perhaps a couple of weeks may be needed before the casts have disintegrated, though any local epithelial damage is repaired earlier. These nephrons may remain relatively non-functioning while the casts are present. The remaining healthy nephrons have thus to carry the whole load of excretion of urine If there are few of these healthy nephrons, each of them is under heavy stress and, abandoning most of its function of concentrating and elaborating the filtrate, it produces a large amount of very dilute urine which may be almost unchanged filtrate. The total volume of this urine produced by the healthy nephrons is of course small. As the damaged nephrons regain their function and take their share in the formation of urine, the total quantity of urine increases considerably. Subsequently, as the concentrating power of the nephrons improves, the quantity and quality of the urine return to normal.

If the kidney damage is such that repair is possible, the purpose of treatment is to ameliorate the biochemical disturbances which may kill the patient before the kidney has time to recover. It seems possible that a number of the fatal cases recorded in the present paper might have been saved if more satisfactory lines of treatment had been available. While the present paper is not concerned with the details of therapy, a brief summary of modern methods may be given here. Considerable success has been achieved in the treatment of cases of anuria (some due to 'lower nephron nephrosis', and some presumably due to proximal convoluted tubule necrosis or the lesser degrees of R.C.N.) by the following regimen (Burwell, Kinney and Finch, 1947; Thorn, 1948; Bull, Joekes and Lowe, 1949; Burt et al., 1950; Kolff, 1950):

(*a*) During the period of anuria, the avoidance of administration of excess

fluid or of electrolytes which can not be excreted (Lattimer, 1945). A Borst diet is given to prevent endogenous protein breakdown.

(*b*) During the period of subsequent diuresis, the correct amounts of water, sodium chloride and potassium are provided, so that the patient does not become dehydrated, and so that the electrolytes of the blood are maintained at a normal level.

Various methods of 'vicarious' excretion of urine have also been used Peritoneal dialysis has the disadvantage of leading to fibrinous exudates, and requires a sterile technique (Fine, Frank and Seligman, 1946; Grossman, Ory and Willoughby, 1947, Odell, Ferris and Power, 1948; Miller, 1949). The 'artificial kidney' requires complex apparatus and strict biochemical control, but has been used extensively and with some good results (Kolff, 1947; Alwall, 1947; Murray, Delorme and Thomas, 1948; Merrill et al, 1950) As the patient's blood must be heparinised, this method can not be used if there is any likelihood of haemorrhage; it is also not very satisfactory in hypertensive [illegible]

[illegible]

as with other dialysis procedures, is a method by which the plasma potassium can be rapidly reduced The ideal intestinal perfusion fluid to maintain a satisfactory water and electrolyte balance has not yet been worked out

Other methods of treating the anuric patient include massive replacement transfusion, as advocated by Dausset (1950). Such therapy in obstetric cases would require very careful blood-grouping

Transplantation of a normal human kidney would theoretically be the only satisfactory treatment for gross R.C N. Even if the transplanted kidney functioned for only a few weeks, it might permit the survival of patients with slightly less severe grades of R C N There are many technical and biological difficulties in this operation, an excellent summary of the problems has been given by Dempster (1950 and 1951) A detailed report of one transplantation for congenital cystic disease is given by Lawler et al. (1950 and 1951), the kidney functioned well for over two months but the ureter subsequently became stenosed and the kidney had atrophied at 10 months. Servelle et al. (1951) transplanted a kidney into a patient with chronic nephritis. The urine output of this kidney increased to 600 cc. on the 19th day, with urine urea concentration about twice that in the blood. The patient died on the 19th day, and at autopsy the kidney appeared normal apart from one small infarct. Dubost et al (1951) did transplantation in two cases of chronic nephritis The cases were reported at 14 days and 3 days later respectively Renal function appeared to be improving, particularly in the case of longer duration

Other lines of treatment are directed to the prevention or amelioration of the pathological lesions in the kidney. These are of very doubtful value when

undertaken more than 12 hours after the U P.A.. Decapsulation is based on the unfounded assumption that the oedema in the kidney a few days after the U.P.A. may prevent a satisfactory circulation of blood. There is no evidence that the few patients who have improved after this operation would not have improved at the same time without operation. This subject has been reviewed by Abeshouse (1945), Peters (1945), and Bracey (1950). Similar considerations apply to surgical or medical therapy designed to relieve vascular spasm, when these measures are applied a few days after the U.P.A.

SUBSEQUENT CONDITION

If the patient recovers, the later changes in the kidney can be inferred from general pathological principles. Any areas of R.C.N. will become gradually replaced by connective tissue. Some of the regenerated tubules atrophy and disappear towards the end of the second week; these will also be replaced by patches of connective tissue. As far as we are aware, there has however been no report of the pathological appearances in the kidneys of patients who, several years previously, have had transient renal failure following U.P.A.

There is not a great deal of information about the ultimate clinical state of these patients. Dieckmann (1942) gives details of a patient who had puerperal oliguria following U.P.A , her urea clearance 9 months later was under 50 per cent, and her blood pressure was 150/100. Crook's patient had a normal urine urea concentration 6 months after the U.P.A.. One patient studied by Crawford (unpublished) had a clinical course corresponding to group *g*, with a blood urea rising to 206 mg per 100 cc. by the 8th day. On the 23rd day, with a blood urea of 40 mg. per 100 cc., her maximum urea clearance was 38 cc., which is about 50 per cent of normal. At 5 months, with a blood urea of 20 mg. per 100 cc., she had a maximum urea clearance of 58 cc., which is about 75 per cent of normal At that time a urea concentration test gave the quite satisfactory figure of 2.9 per cent. Case 1 of Groen and Lindeboom (1940) had a maximum urea clearance of 52 cc. at 3 months, and of 61 cc. at 2 years; their Case 2 had a urea clearance of only about 13 cc. at 4 months.

[illegible] ent of [illegible] It is, [illegible] high incidence of hypertension in patients before the U.P.A.

SUMMARY

In order to obtain information about the course of development of renal cortical necrosis and its related lesions, the kidneys of 67 fatal cases of concealed accidental haemorrhage were examined at various times after the onset of the obstetric catastrophe

In this material there were 23 cases of the fully developed stage of renal cortical necrosis, observed at intervals from 1½ to 15 days This condition is classified here according to its extent: *focal*, affecting scanty minute areas; *minor*, *patchy*; and *gross*, which involves almost all the cortex.

There were 11 examples of the early stages of renal cortical necrosis, examined at intervals from 8 to 27 hours after its onset This stage of the lesion has been recorded only very rarely in the previous literature.

In addition, a series of less severe renal lesions were observed in 26 of the remaining cases. These lesions consisted of (*a*) albuminuria with cast formation in collecting tubules, (*b*) hyaline droplet formation in proximal convoluted tubules, (*c*) colloid degeneration and colloid necrosis of the epithelium of these tubules, (*d*) the formation of colloid casts in the tubules of the intermediate zone, (*e*) simple necrosis of proximal convoluted tubules, (*f*) benign thrombosis of glomerular capillaries Great importance is attached to this series of lesions which are less severe than renal cortical necrosis. Clinically, certain of them can give rise to anuria and sometimes to the death of the patient Pathologically, their significance is that they are due to the same type of vascular disturbance which gives rise to renal cortical necrosis, and that they throw much light on the nature of this vascular disturbance

All the renal lesions result from ischaemia which is produced by spasm of some part of the cortical arterial tree, and the type of the lesions depends on the duration and the site of this spasm The exact aetiology of this spasm is as yet not clear

The damage to the kidney begins very quickly after the onset of the concealed accidental haemorrhage. The exact time of the onset of the renal lesions can thus be established from the obstetric history Cases have been examined at a series of known intervals after the onset; in this way the course of development of each type of renal lesion has been established, with particular reference to the progress of the histological changes at different times.

The course of the circulatory changes in the kidney is as follows. In all cases there is an initial spasm at the glomeruli, which cuts off the blood flow for a period of time varying from a few minutes up to 5 or 6 hours. After this period the spasm relaxes, and blood recirculates through the area. If the recirculation begins early and continues permanently, the cases have purely

tubular lesions. On the other hand, in cases destined to become renal cortical necrosis, a new spasm develops in some part of the intralobular artery. This produces a second period of ischaemia, which may last from a few hours up to about 20 to 30 hours, and which leads to death of all the distal part of the arterial tree. When the arterial spasm relaxes, the blood flows into the dead *arteries and undergoes thrombosis there, thus leading* to a permanent arrest of the circulation. This thrombosis is a late secondary phenomenon, and is a result, not a cause, of the ischaemia

In the previous literature on renal lesions following concealed accidental haemorrhage, there are 74 reliable cases of renal cortical necrosis, 49 poorly described cases of renal cortical necrosis, and 22 cases of less severe damage to the kidney These have been classified in accordance with the present scheme.

The clinical manifestations of each type of case, as observed both in the present series and in the literature, have also been analysed, with special reference to the changes in the urine and the blood Of the patients who have severe concealed accidental haemorrhage, about 7.5 per cent die during the first day, and half of these have very severe renal damage in an early stage. A further 3 5 per cent die later in the puerperium, mainly as a result of renal failure from the developed stage of renal cortical necrosis. The incidence of severe damage to the kidney is greatest in patients with concealed accidental haemorrhage at about 6 or 7 months gestation.

In cases of renal cortical necrosis, the prognosis depends both upon the amount of the remaining part of the cortex, and on the degree of the ischaemic damage which it has sustained. In this remaining part, there is always much necrosis or epithelial degeneration in the proximal convoluted tubules, and there is often much cast formation in other tubules. Patients with only a small amount of actual renal cortical necrosis may die in anuria as a result of the damage to this other part of the kidney.

The prevention of these lesions depends upon the arrest of the spasm in the arterial tree before gross renal damage has occurred; i.e. within the first 2 or 3 hours after the accidental haemorrhage if necrosis of the proximal convoluted tubules is to be averted, and within the first 6 or 8 hours if renal cortical necrosis is to be averted.

Renal cortical necrosis occurs also after abortions, in various conditions in children, in adult men, and in non-pregnant women. A total of 7 of these cases have been studied, for comparison with the obstetric series, and 117 previous reports in the literature have been analysed. These non-obstetric cases are sometimes of a particular type, which is described in this paper as confluent focal renal cortical necrosis.

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